WO9807742

Publication Title:

SULFONAMIDES

Abstract:

Abstract of WO9807742

Compounds of formula (I) wherein R<1> is aryl, heterocyclyl or heteroaryl; R<2> is hydrogen, C1-8alkyl, C2-6alkenyl, C2-6alkynyl, C3-8cycloalkyl, heteroaryl, heterocyclyl, arylC1-6alkyl, heteroarylC1-6alkyl, heterocyclylC1-6alkyl or C3-8cycloalkylC1-6alkyl; R<3> is C1-6alkyl, C2-6alkenyl, aryl, C1-6alkyl, heteroarylC1-6alkyl or the side-chain of a naturally occurring amino acid; R<4> is hydrogen, C1-6alkyl, C3-8cycloalkyl, C4-8cycloalkenyl, arylC1-6alkyl, heteroarylC1-6alkyl or heterocyclylC1-6alkyl; R<5> is hydrogen or C1-6alkyl; or R<4> and R<5> together with the nitrogen atom to which they are joined form a heterocyclic ring; wherein any group or ring, in R<1>-R<5>, is optionally substituted; or pharmaceutically acceptable salts or in vivo hydrolysable esters thereof, are described as inhibitors of the production of Tumor Necrosis Factor and/or one or more matrix metalloproteinase enzymes. Compositions containing them and their preparation are also described. Data supplied from the esp@cenet database - Worldwide

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 5/06, C07C 311/22 | A1

(11) International Publication Number: WO 98/07742

(43) International Publication Date: 26 February 1998 (26.02.98)

(21) International Application Number: PCT/GB97/02222

(22) International Filing Date: 19 August 1997 (19.08.97)

(30) Priority Data:
96401815.4 23 August 1996 (23.08.96) EP
(34) Countries for which the regional or international application was filed: FR et al.
96402031.7 25 September 1996 (25.09.96) EP
(34) Countries for which the regional or international application was filed: FR et al.

(71) Applicants *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). ZENECA-PHARMA S.A. [FR/FR]; "Le Galien", 1, rue des Chauffours, Boîte postale 127, F-95022 Cergy Cedex (FR).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BARLAAM, Bernard, Christophe [FR/FR]; Zeneca Pharma, Centre de Recherches, Z.I. La Pompelle, Chemin de Vrilly, Boîte postale 1050, F-51689 Reims Cedex 2 (FR).

(74) Agent: DENERLEY, Paul, Millington; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

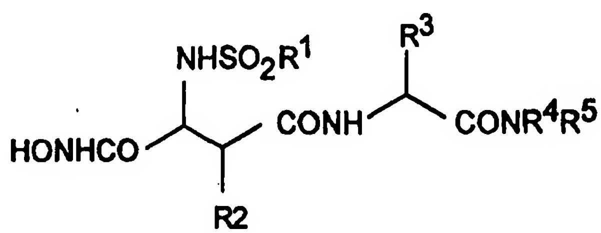
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: SULFONAMIDES

(57) Abstract

Compounds of formula (I) wherein R^1 is aryl, heterocyclyl or heteroaryl; R^2 is hydrogen, C_{1-8}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, heteroaryl, heterocyclyl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, heterocyclylC_{1-6}alkyl or C_{3-8}cycloalkylC_{1-6}alkyl; R^3 is C_{1-6}alkyl, C_{2-6}alkenyl, aryl, C_{1-6}alkyl, heteroarylC_{1-6}alkyl or the side-chain of a naturally occurring amino acid; R^4 is hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{4-8}cycloalkenyl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl or heterocyclylC_{1-6}alkyl; R^5 is hydrogen or C_{1-6}alkyl; or R^4 and R^5 together with the nitrogen atom to which they are joined form a heterocyclic ring; wherein any group or ring, in R^1-R^5, is optionally substituted; or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, are described as inhibitors of the production of Tumor Necrosis Factor and/or one or more matrix metalloproteinase enzymes. Compositions containing them and their preparation are also described.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

SULFONAMIDES

This invention relates to sulfonamides and in particular to sulfonamides wherein the sulfonamide group is located adjacent to a hydroxamate group. This invention further relates to processes for preparing such sulfonamides, to pharmaceutical compositions containing them and to their use in methods of therapeutic treatment.

The compounds of this invention are inhibitors of the production of TNF (Tumour Necrosis Factor) which is believed to be formed by the cleavage of a pro-form, or larger precursor, by the enzyme pro-TNF Convertase. Applicants believe that the compounds of the present invention inhibit TNF production by mechanisms which include inhibition of pro-TNF Convertase. The term 'TNF' is used herein to refer to Tumour Necrosis Factor in general but, in particular, to TNFα.

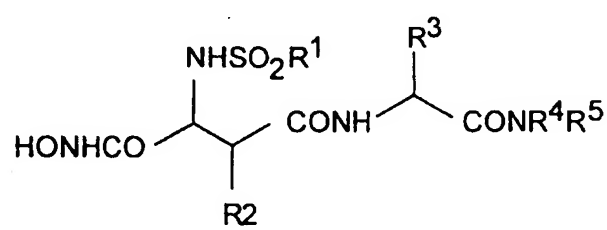
The compounds of this invention will be useful in the treatment of disease or medical conditions in which excessive TNF production is known to give rise via a cascade of processes to a variety of physiological sequelae including the production of physiologically-active eicosanoids such as the prostaglandins and leukotrienes, the stimulation of the release of proteolytic enzymes such as collagenase, the activation of osteoclast activity leading to the resorption of calcium, the stimulation of the release of proteoglycans from, for example, cartilage, the stimulation of cell proliferations and to angiogenesis. It is also known that, in certain cellular systems, TNF production precedes and mediates the production of other cytokines such as interleukin-1 (IL-1) and interleukin-2 (IL-2) which are also believed to contribute to the pathology of disease states such as inflammatory and allergic diseases and cytokine-induced toxicity. Excessive TNF production has also been implicated in mediating or exacerbating the development of various inflammatory and allergic diseases such as inflammation of the joints (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastrointestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), skin disease (especially psoriasis, eczema and dermatitis) and respiratory disease (especially asthma, bronchitis and allergic rhinitis), and in the production and development of various cardiovascular disorders such as myocardial infarction, angina and peripheral vascular disease. Excessive TNF production has also been implicated in mediating complications of bacterial, fungal and/or viral infections such as endotoxic shock, septic

shock and toxic shock syndrome. Excessive TNF production has also been implicated in mediating or exacerbating the development of adult respiratory distress syndrome, diseases involving cartilage or muscle resorption, Paget's disease and osteoporosis, pulmonary fibrosis, cirrhosis, renal fibrosis, the cachexia found in certain chronic diseases such as malignant disease and acquired immune deficiency syndrome (AIDS), tumour invasiveness and tumour metastasis and multiple sclerosis.

The compounds of the invention may also be inhibitors of one or more matrix metalloproteinases such as collagenases, stromelysins and gelatinases. Thus they may also be of use in the therapeutic treatment of disease conditions mediated by such enzymes for example arthritis (rheumatoid and osteoarthritis), osteoporosis and tumour metastatis.

The present invention provides novel sulfonamides which have activity as inhibitors of TNF and/or are inhibitors of one or more matrix metalloproteinase enzymes.

Accordingly the present invention provides a compound of the formula (I):



(I)

wherein:

R^1 is is aryl, heterocyclyl or heteroaryl;

R^2 is is hydrogen, C_{1-8}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, aryl, heteroaryl, heterocyclyl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, heterocyclylC_{1-6}alkyl or C_{3-8}cycloalkylC_{1-6}alkyl;

R^3 is C_{1-6}alkyl, C_{2-6}alkenyl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl or the side-chain of a naturally occurring amino acid;

R^4 is hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{4-8}cycloalkenyl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl or heterocyclylC_{1-6}alkyl;

R^5 is hydrogen or C_{1-6}alkyl; or R^4 or R^5 together with the nitrogen atom to which they are joined form a heterocyclic ring;

wherein any group or ring, in R^1-R^5, is optionally substituted;

or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof.

"Aryl in the terms "aryl" and "arylC_{1-6}alkyl" typically means phenyl or naphthyl, preferably phenyl. "Heteroaryl" in the terms "heteroaryl" and "heteroarylC_{1-6}alkyl" means an aromatic mono- or bicyclic 5-10 membered ring with up to five ring heteroatoms selected from nitrogen, oxygen and sulphur. Examples of 'heteroaryl' include thienyl, pyrrolyl, furanyl, imidazolyl, thiazolyl, pyrimidinyl, pyridinyl, indolyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl. "Heterocyclyl" in the terms "heterocyclyl" and "heterocyclyl C_{1-6}alkyl" means a non-aromatic mono- or bicyclic 5-10 membered ring with up to five ring hetero atoms selected from nitrogen, oxygen and sulphur. Examples of 'heterocyclyl' include pyrrolidinyl, morpholinyl, piperidinyl, dihydropyridinyl and dihydropyrimidinyl.

Any group or ring in R^1-R^5 may be optionally substituted, for example by up to five substituents, preferably up to three substituents which may be the same or different. Typical substituents include: hydroxy, C_{1-6}alkoxy for example methoxy, mercapto, C_{1-6}alkylthio for example methylthio, amino, C_{1-6}alkylamino for example methylamino, di-(C_{1-6}alkyl)amino for example dimethylamino, carboxy, carbamoyl, C_{1-6}alkylcarbamoyl for example methylcarbamoyl, di-C_{1-6}alkylcarbamoyl for example dimethylcarbamoyl, C_{1-6}alkylsulphonyl for example methylsulphonyl, arylsulphonyl for example phenylsulphonyl, C_{1-6}alkylaminosulphonyl for example methylaminosulphonyl, di-(C_{1-6}alkyl)aminosulphonyl for example dimethylaminosulphonyl, nitro, cyano, cyano-C_{1-6}alkyl for example cyanomethyl, hydroxyC_{1-6}alkyl for example hydroxymethyl, amino-C_{1-6}alkyl for example aminoethyl, C_{1-6}alkanoylamino for example acetamido, C_{1-6}alkoxycarbonylamino for example methoxycarbonylamino, C_{1-6}alkanoyl for example acetyl, C_{1-6}alkanoyloxy for example acetoxy, C_{1-6}alkyl for example methyl, ethyl, isopropyl or tert-butyl, halo for example fluoro, chloro or bromo, trifluoromethyl, aryl for example phenyl, arylC_{1-6}alkyl for example benzyl, aryloxy for example phenoxy, arylC_{1-6}alkoxy for example benzyloxy, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl. A further typical substituent is trifluoromethoxy. The term "side chain of a naturally occurring amino acid" means the side chain X of an amino acid NH_2-CHX-COOH. Suitable amino acids include alanine, arginine,

aspartic acid, cysteine, asparagine, glutamine, histidine, homoserine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, serine, threonine, tryptophan, tyrosine and valine.

The compounds of the present invention possess a number of chiral centres, at $-CH(NHSO_2R^1)-$, at $-CHR^3-$, at $-CHR^2-$ (when R^2 is not hydrogen) and possibly in the variables R^1-R^5. The present invention covers all diastereoisomers and mixtures thereof that inhibit TNF Convertase and/or inhibit matrix metalloproteinase enzymes.

Suitably R^1 is an optionally substituted phenyl group or optionally substituted naphthyl group. Favourably R^1 is phenyl or naphthyl wherein either ring is unsubstituted or substituted by one or two groups selected from halogen for example chloro or fluoro, C_{1-6}alkylcarbonyl for example acetyl, C_{1-6}alkanoylamino for example acetamido, trifluoromethyl, cyano, C_{1-6}alkyl for example methyl, isopropyl or tert-butyl, trifluoromethoxy, carboxy, nitro, di-C_{1-6}alkylamino for example dimethylamino or is C_{1-6}alkoxy for example methoxy.

In one aspect R^1 is phenyl or naphthyl wherein either ring is unsubstituted or substituted by one or two groups selected from halogen for example chloro or fluoro, C_{1-6}alkylcarbonyl for example acetyl, C_{1-6}alkanoylamino for example acetamido, trifluoromethyl, cyano, C_{1-6}alkyl for example methyl, isopropyl or tert-butyl, or is C_{1-6}alkoxy for example methoxy.

Preferably R^1 is phenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 2-cyanophenyl, 3,5-difluorophenyl, 4-acetylphenyl, 4-acetamidophenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl or 3,5-dichlorophenyl. Preferably also R^1 is 2,4,6-trimethylphenyl, 3-trifluoromethyl, 4-carboxyphenyl, 4-bromophenyl, 3-chlorophenyl, 2-chloro-4-fluorophenyl, 4-isopropylphenyl, 3-nitrophenyl, 3-carboxyphenyl or 2,4,6-tri-isopropylphenyl. Most preferably R^1 is phenyl or 4-acetylphenyl.

Preferably also R^1 may be naphth-1-yl or naphth-2-yl or naphthyl optionally substituted such as 5-dimethylaminonaphth-1-yl or 5-dimethylaminonaphth-2-yl.

In another aspect suitably R^1 is an optionally substituted heteroaryl group as hereinbefore defined. More particularly R^1 is an optionally substituted heteroaryl group wherein the heteroaryl group has 5 or 6 ring atoms, one to three of which are selected from

nitrogen and sulphur or is a bicyclic derivative thereof wherein two adjacent carbon atoms are fused to a benzene ring.

Examples of R^1 being a monocyclic heteroaromatic ring include pyridazinyl, pyrimidinyl, pyridinyl, triazolyl, imidazolyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl and isoxazolyl, any of which may be optionally substituted for example by C_{1-6}alkyl such as methyl, halo such as chloro, fluoro or bromo, phenyl or pyridinyl. In one aspect R^1 is pyridazinyl, pyrimidinyl, pyridinyl, triazolyl, imidazolyl, thienyl, pyrrolyl or thiazolyl.

Preferably R^1 is a bicyclic heteroaromatic ring system wherein one or both rings may contain ring heteroatoms and wherein the sulfonamide link may be to either ring. Favourably one ring is a benzene ring fused on two adjacent carbon atoms to a 5- or 6-membered nitrogen containing ring which ring may be saturated or unsaturated. Examples of such favoured ring systems include quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, quinazolinyl, 3,4-dihydroquinazolinyl, indolyl, benzofuranyl, benzthiazolyl, benzofurazanyl and isoindolyl. Suitably such ring systems may be optionally substituted as described hereinbefore, in particular by C_{1-6}alkyl for example methyl and by oxo (= O). Particular ring systems include quinolin-8-yl, quinolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl, oxindol-5-yl, isoquinolin-5-yl, 1,2,3,4-tetrahydroquinolin-8-yl, 4-oxo-3,4-dihydroquinazolin-8-yl and 4-oxo-3,4-dihydroquinazolin-6-yl.

In a further aspect R^1 may be an optionally substituted heterocyclyl group as hereinbefore defined. More particularly R^1 is an optionally substituted heterocyclyl group having 5 or 6 ring atoms, one to three of which are selected from nitrogen, oxygen or sulphur. Examples of particular heterocyclyl groups include tetrahydropyran, tetrahydrofuran, piperidine and bicyclic derivatives thereof wherein two adjacent carbon atoms are fused to another ring.

There is a chiral centre at -CH($NHSO_2R^1$); it is preferred that this centre has the configuration indicated in formula (II) hereinafter. For most values of R^1 this centre will have the S-stereochemistry under the Cahn-Prelog-Ingold sequence rules.

Particular groups for R^2 include C_{1-8}alkyl for example isopropyl, n-propyl, isobutyl, sec-butyl, n-butyl, tert-butyl, isopentyl, n-pentyl, hexyl, heptyl or octyl; C_{1-8}alkyl interrupted by an oxygen or sulphur atom for example methoxypropyl, ethoxyethyl, propoxymethyl, ethylthioethyl, methylthiopropyl; phenylC_{1-6}alkyl for example benzyl, phenethyl,

phenylpropyl or phenylbutyl; phenylC_{1-6}alkyl wherein the alkyl chain is interrupted by oxygen or sulphur for example benzyloxypropyl and benzyloxybutyl; C_{3-8}cycloalkyl for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; or C_{3-8}cycloalkylC_{1-6}alkyl for example cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl or cyclohexylmethyl.

In a particular aspect R^2 may be C_{1-8}alkyl for example isopropyl, n-propyl, isobutyl, sec-butyl, n-butyl, tert-butyl, isopentyl, n-pentyl, hexyl, heptyl or octyl; C_{1-8}alkyl interrupted by an oxygen or sulphur atom for example methoxypropyl, ethoxyethyl, propoxymethyl, ethylthioethyl or methylthiopropyl; phenylC_{1-6}alkyl for example benzyl, phenethyl, phenylpropyl or phenylbutyl; C_{3-8}cycloalkyl for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; or C_{3-8}cycloalkylC_{1-6}alkyl for example cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl or cyclohexylmethyl.

Preferably R^2 is isobutyl.

There is a chiral centre at -CHR^2- (when R^2 is not hydrogen); it is preferred that this centre has the configuration indicated in formula (II) hereinafter. For most values of R^2 this centre will have the R-stereochemistry under the Cahn-Prelog-Ingold sequence rules.

Particular groups for R^3 include C_{1-6}alkyl for example methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl, isopentyl, n-pentyl or hexyl; C_{1-6}alkyl interrupted by an oxygen or sulphur atom for example methoxyethyl, methoxypropyl, methylthioethyl or 1,1-dimethylmethylthiomethyl ($MeSCMe_2$-); or phenylC_{1-6}alkyl for example benzyl or phenethyl.

Preferably R^3 is isobutyl, tert-butyl, 1,1-dimethylmethylthiomethyl or benzyl with tert-butyl being most preferred.

The chiral centre at -CHR^3- preferably has the configuration indicated in formula (II) hereinafter. For most of R^3 this centre will have the S-stereochemistry.

Particular groups for R^4 include C_{1-6}alkyl for example methyl, ethyl, n-propyl, isopropyl, tert-butyl or n-butyl; C_{1-6}alkyl interrupted by an oxygen or sulphur atom for example hydroxyethyl, methoxyethyl, methylthioethyl or ethoxyethyl; phenylC_{1-6}alkyl for example benzyl, phenethyl or phenylpropyl; or C_{3-8}cycloalkylC_{1-6}alkyl for example cyclopropylmethyl, cyclobutylmethyl or cyclopentylmethyl.

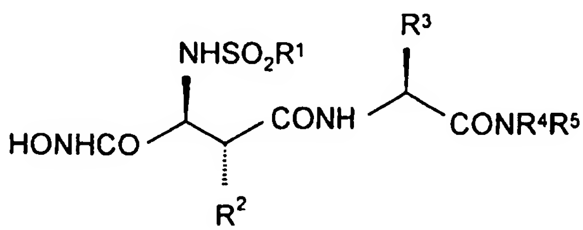
Particularly also, R^4 may be C_{1-6}alkylaminoC_{2-6}alkyl for example methylaminoethyl, di-C_{1-6}alkylaminoC_{2-6}alkyl for example dimethylaminoethyl or dimethylaminopropyl, or is heterocyclicC_{1-6}alkyl for example 2-morpholinoethyl, 2-piperidinoethyl, 2-piperazinoethyl or 2-(N-methyl)piperazinoethyl.

Preferably R^4 is methyl, ethyl, n-propyl, isobutyl, tert-butyl, dimethylaminoethyl, dimethylaminopropyl, morpholinoethyl or benzyl. Of these methyl is most preferred.

Particular groups for R^5 are hydrogen and C_{1-6}alkyl for example methyl or ethyl. Preferably R^5 is hydrogen.

In another aspect R^4 and R^5 together with the nitrogen atom to which they are joined form a heterocyclic ring, for example a 5 or 6 membered heterocyclic ring such as morpholino, piperidino, piperazino or N-methylpiperazino. Of these morpholino is preferred.

A particularly suitable class of compounds of the present invention is that of formula (II):



(II)

wherein R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined.

A preferred class of compounds of the formula (II) is that wherein R^1 is phenyl or naphthyl either being unsubstituted or substituted by one or two groups selected from halogen for example chloro or fluoro, C_{1-6}alkylcarbonyl for example acetyl, C_{1-6}alkanoylamino for example acetamido, trifluoromethyl, cyano, C_{1-6}alkyl for example methyl, isopropyl or tert-butyl, trifluoromethoxy, carboxy, nitro, di-C_{1-6}alkylamino for example dimethylamino or is C_{1-6}alkoxy for example methoxy;

or R^1 is pyridazinyl, pyrimidinyl, pyridinyl, triazolyl, imidazolyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl or oxazolyl any of which is unsubstituted or substituted by C_{1-6}alkyl for example methyl, halo for example chloro, fluoro or bromo, phenyl or pyridinyl;

or R^1 is quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, quinazolinyl, 3,4-dihydroquinazolinyl, indolyl, benzofuranyl, benzothiazolyl, benzofurazanyl or isoindolyl any of which is unsubstituted or substituted by C_{1-6}alkyl for example methyl and/or oxo(= O);
R^2 is isobutyl;
R^3 is isobutyl, tert-butyl, 1,1-dimethylmethylthiomethyl or benzyl;
R^4 is methyl, ethyl, n-propyl, isobutyl, tert-butyl, dimethylaminoethyl, dimethylaminopropyl, 2-morpholinoethyl or benzyl; and R^5 is hydrogen or methyl; or R^4 and R^5 together with the nitrogen atom to which they are joined form a morpholine ring.

In one aspect a preferred class of compounds of the formula (II) is that wherein R^1 is phenyl or naphthyl unsubstituted or substituted by one or two groups selected from halogen for example chloro or fluoro, C_{1-6}alkylcarbonyl for example acetyl, C_{1-6}alkanoylamino for example acetamido, trifluoromethyl, cyano, C_{1-6}alkyl for example methyl, isopropyl or tert-butyl or C_{1-6}alkoxy for example methoxy; R^3 is isobutyl, 1,1-dimethylmethylthiomethyl, tert-butyl or benzyl; R^4 is methyl, ethyl, n-propyl, isobutyl, tert-butyl or benzyl; and R^5 is hydrogen.

A particular class of preferred compounds is that wherein R^1 is quinolin-8-yl, quinolin-6-yl, 1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl, oxindol-5-yl, isoquinolin-5-yl, 1,2,3,4-tetrahydroquinolin-8-yl, 4-oxo-3,4-dihydroquinazolin-8-yl or 4-oxo-3,4-dihydroquinazolin-6-yl;
R^2 is isobutyl;
R^3 is isobutyl, tert-butyl, 1,1-dimethylmethylthiomethyl or benzyl;
R^4 is methyl, ethyl, n-propyl, isobutyl, tert-butyl, dimethylaminoethyl, dimethylaminopropyl, 2-morpholinoethyl or benzyl; and R^5 is hydrogen or methyl; or R^4 and R^5 together with the nitrogen atom to which they are joined form a morpholine ring.

Suitable pharmaceutically acceptable salts include acid addition salts such as hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine.

In vivo hydrolysable esters are those pharmaceutically acceptable esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified

by administering, for example intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable in vivo hydrolysable esters for carboxy include methoxymethyl and for hydroxy include acetyl.

In order to use a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically acceptable salt or an in vivo hydrolysable ester and pharmaceutically acceptable carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to hereinabove.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.5 to 75 mg/kg body weight (and preferably of 0.5 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

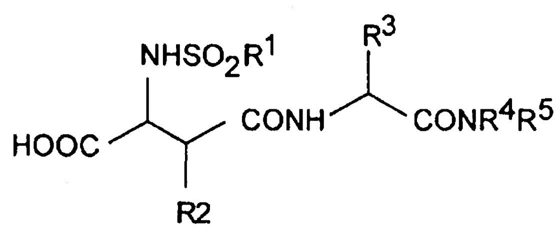
Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

Therefore in a further aspect, the present invention provides a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect the present invention provides a method of treating a disease condition mediated by TNF which comprises administering to a warm-blooded animal an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof. The present invention also provides the use of a compound of the formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof in the preparation of a medicament for use in a disease condition mediated by TNF.

In another aspect the present invention provides a process for preparing a compound of the formula or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof which process comprises

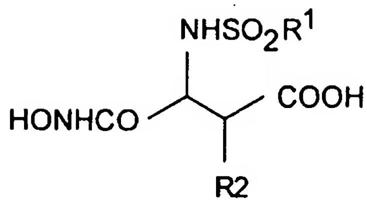
a) reacting a compound of the formula (III):



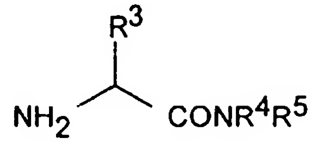
(III)

wherein R^1-R^5 are as hereinbefore defined, or an activated derivative thereof with hydroxylamine, O-protected hydroxylamine or a salt thereof; or

b) coupling a compound of the formula (IV) with a compound of the formula (V):



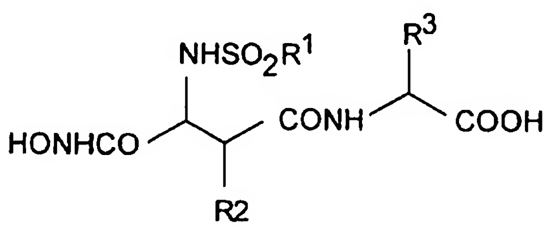
(IV)



(V)

wherein R^1-R^5 are as hereinbefore defined, under standard peptide coupling conditions; or

c) reacting a compound of the formula (VI) with compound of the formula (VII):



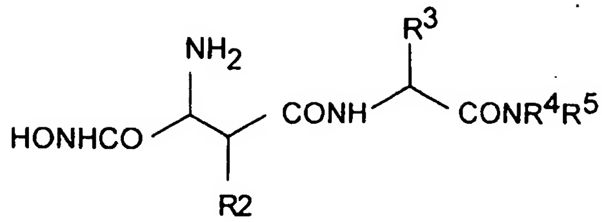
(VI)

NHR^4R^5

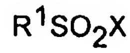
(VII)

or

d) reacting a compound of the formula (VIII) with a compound of the formula (IX):



(VIII)



(IX)

wherein R^1-R^5 are as hereinbefore defined and X is a leaving group:

wherein any functional group is protected, if necessary, and:

i. removing any protecting groups;

ii. optionally forming a pharmaceutically acceptable salt or in vivo hydrolysable ester.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question, and may be introduced by conventional methods.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxyl protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (eg isopropyl, t-butyl); lower alkoxy lower alkyl groups (eg

methoxymethyl, ethoxymethyl, isobutoxymethyl); lower aliphatic acyloxy lower alkyl groups, (eg acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (eg 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (eg benzyl, p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (eg trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (eg trimethylsilylethyl); and (2-6C)alkenyl groups (eg allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxyl protecting groups include lower alkyl groups (eg t-butyl), lower alkenyl groups (eg allyl); lower alkanoyl groups (eg acetyl); lower alkoxycarbonyl groups (eg t-butoxycarbonyl); lower alkenyloxycarbonyl groups (eg allyloxycarbonyl); aryl lower alkoxycarbonyl groups (eg benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (eg trimethylsilyl, t-butyldimethylsilyl) and aryl lower alkyl (eg benzyl) groups.

Examples of amino protecting groups include formyl, aralkyl groups (eg benzyl and substituted benzyl, p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (eg t-butoxycarbonyl); lower alkenyloxycarbonyl (eg allyloxycarbonyl); aryl lower alkoxycarbonyl groups (eg benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); trialkylsilyl (eg trimethylsilyl and t-butyldimethylsilyl); alkylidene (eg methylidene); benzylidene and substituted benzylidene groups.

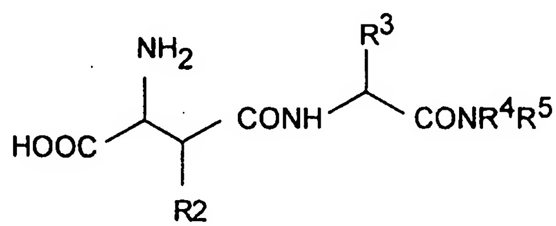
Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis, for groups such as p-nitrobenzyloxycarbonyl, hydrogenation and for groups such as o-nitrobenzyloxycarbonyl, photolytically.

Compounds of the formula (I) may be converted to other compounds of the formula (I) by standard chemical methodologies, for example hydrogenation of a quinoline to a 1,2,3,4-tetrahydroquinoline.

The hydroxylamine group (HONH-), in particular in process variants (b), (c) and (d), is typically O-protected for example with benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, t-butyl or a silyl (for example trimethylsilyl) group.

In process variant a), the compound of the formula (III) may be reacted in the form of the acid or an activated derivative thereof such as an acid halide, acid anhydride or an 'activated' ester such as 1H-benzo[1,2,3]triazol-1-yl, 1-hydroxy-benzo[1,2,3]triazole, pentafluorophenyl or 2,4,5-trichlorophenyl in the presence of a carbodiimide. The reaction of the compound of the formula (III) and hydroxylamine is performed under standard conditions. Typically the reaction of an activated ester of a compound of the formula (III) and hydroxylamine or O-protected hydroxylamine is performed in the presence of a base, for example 2,6-lutidine (optionally in the presence of dimethylaminopyridine) or N-methylmorpholine in an anhydrous aprotic solvent, for example dimethylformamide, at a non-extreme temperature, for example in the region -30° to +25°, preferably about 0°C.

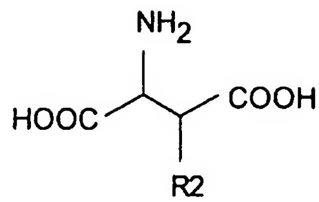
The compound of the formula (III) may be prepared by reacting a compound of the formula (IX) with a compound of the formula (X):



(X)

wherein R^2-R^5 are as hereinbefore defined and wherein the carboxylic acid function is typically protected, for example by a tert-butyl group, which protection is removed subsequent to the reaction. The conditions for reacting the compounds of the formula (IX) and (X) are similar to those described hereinafter for the reaction of compounds of the formulae (VIII) and (IX).

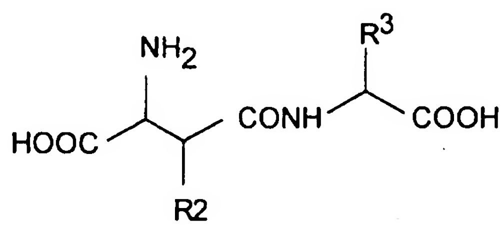
The compounds of the formula (X), optionally with the carboxylic acid function protected, may be prepared by coupling a suitably protected compound of the formula (XI):



(XI)

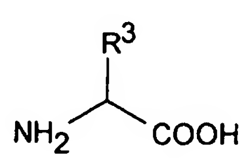
wherein R^2 is as hereinbefore defined, with a compound of the formula (V). The compounds of the formula (XI) may be prepared in standard manner, for example by the alkylation of protected aspartic acid derivatives or by the reaction of a glycine nucleophilic equivalent with a compound of the formula: R^2-CHX^1-COOH (protected as necessary) wherein X^1 is a leaving group for example a triflate.

In an alternative the compounds of the formula (X), optionally with the carboxylic acid function protected, may be prepared by coupling a suitably protected compound of the formula (XII):



(XII)

wherein R^2 and R^3 are as hereinbefore defined, with a compound of the formula (VII). The compounds of the formula (XII) may be prepared by coupling suitably protected compounds of the formulae (XI) and (XIII):

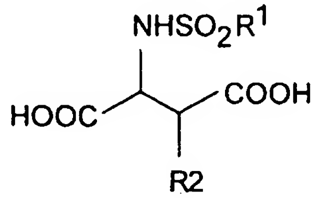


(XIII)

wherein R^3 is as hereinbefore defined.

In process variant b), the compounds of the formulae (IV) and (V) are reacted under standard peptide coupling conditions wherein any functional group is protected as necessary.

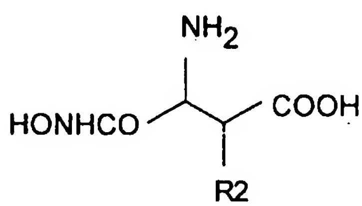
The compounds of the formula (IV) may be prepared by reacting a suitably protected compound of the formula (XIV):



(XIV)

wherein R^1 and R^2 are as hereinbefore defined with hydroxylamine in a manner similar to that described hereinabove for converting a compound of the formula (III) to a compound of the formula (I). The compounds of the formula (XIV) may be prepared by reacting a compound of the formula (XI) with a compound of the formula (IX).

In an alternative the compounds of the formula (IV) may be prepared by reacting a suitably protected compound of the formula (XV):



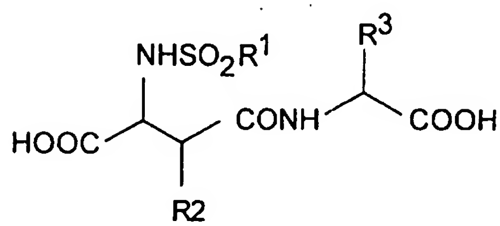
(XV)

wherein R^2 is as hereinbefore defined, with a compound of the formula (IX). The compounds the formula (XV) may be prepared by reacting a compound of the formula (XI) with hydroxylamine in a manner similar to that described hereinabove.

The compounds of the formula (V) may be prepared by reacting a compound of the formula (XIII) with a compound of the formula (VII) under standard coupling conditions.

In process variant c), the compounds of the formulae (VI) and (VII) are reacted under standard conditions for acylation of an amine with any functional groups protected as necessary.

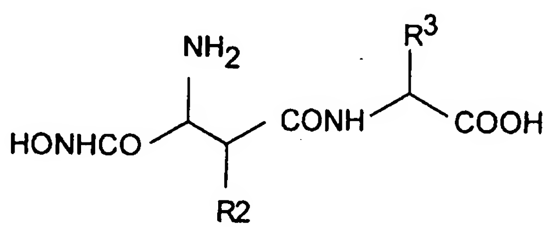
The compounds of the formula (VI) may be prepared by reacting a compound of the formula (XVI):



(XVI)

wherein R^1-R^3 are as hereinbefore defined, with hydroxylamine in a manner similar to that described above. The compounds of the formula (XVI) may be prepared by reacting compounds of the formulae (IX) and (XII) or by reacting compounds of the formulae (XIII) and (XIV) under conditions similar to those described above for similar reactions.

The compounds of the formula (VI) may also be prepared by reacting compounds of the formula (IV) and (XIII) or by reacting compounds of the formulae (IX) and (XVII):



(XVII)

wherein R^2 and R^3 are as hereinbefore defined. The compounds of the formula (XVII) may be prepared by reacting compounds of the formula (XII) with hydroxylamine.

In process variant d), the compounds of the formula (VIII) and (IX) are reacted under standard conditions for sulphonylation of an amine with any functional groups protected as necessary. In the compounds of the formula (IX) X is a leaving group. Preferably X is halo for example fluoro, chloro or bromo, or X is an anhydride-forming group or an ester-forming group. Most favourably X is chloro or bromo. The compounds of the formula (VIII) may be prepared by reacting compounds of the formulae (V) and (XV), or by

reacting compounds of the formulae (XVII) and (VII), or by reacting a compound of the formula (X) with hydroxylamine.

The following biological test methods, data and Examples serve to illustrate the present invention.

Isolated Enzyme Assay

The ability of the compounds of this invention to inhibit proTNFα convertase enzyme is assessed in an isolated enzyme assay (termed "CON2"). Partially purified proTNFα convertase enzyme is obtained from the membranes of THP-1 cells as follows. 1.5-2.0x10^6 cells/ml THP-1 cells (initially cultured in RPMI 1640 medium + 10%(v/v) FCS, 10%(v/v) M1, 2mM L-glutamine 100IU/ml penicillin and 100μg/ml streptomycin) are induced in RPMI 1640 containing 1μg/ml LPS (E. coli O111:B4), 2mM Hydroxyurea, 50μg/ml silica and 1%(v/v) FCS at 37°C in a humidified (5%CO_2/95%air) incubator. After 16 hours the cells are harvested from a 5L induction by centrifugation at 640xg for 15 minutes. The cell pellets are washed once in RPMI 1640 without additive (1L per 2x10^{10} cells) and re-centrifuged at 640xg for 10 minutes. Cell pellets are resuspended in 10mM sodium phosphate buffer pH 7.4, containing 1mM $MgCl_2$, 30mM NaCl, 5μM PMSF, 0.02%(w/v) sodium azide (Buffer A) plus a few micrograms DNAase using 3 times the volume of buffer to packed cell pellets. A polytron homogeniser is used to lyse the cells by 5x5sec bursts with 1-2 minutes cooling between each burst. 30 ml of this homogenate is layered onto 10 mls of 41% (w/v) sucrose made in Buffer A and centrifuged at 150,000xg for 1 hour in a swing out rotor. The membrane is collected from the interphase, diluted by addition of 4 volumes Buffer A and centrifuged at 150,000xg for 20 minutes. The pellet is then resuspended in Buffer A containing 1%(w/v) Triton X-100 to a concentration of 1mg/ml and mixed for 1 hour at 4°C. The solubilised protein is recovered by centrifugation for 30 minutes at 100,000xg at 4°C. The supernatant is applied to a 25ml gelatin-sepharose 4B column equilibrated in 10mM Tris-HCl pH 8.0, 100mM NaCl, 0.1%(w/v) Triton X-100, 200μM PMSF, 0.02%(w/v) azide, 1μM $ZnCl_2$ (Buffer B). After loading the column is washed with Buffer B. The gelatin-sepharose flowthrough plus the first 10mls of the wash is then recycled overnight (1ml/min) on a 30ml wheatgerm-sepharose column previously equilibrated in 10mM Tris-HCl pH 8.0, 0.1%(w/v) Triton X-100, 200μM PMSF, 0.02%(w/v)

azide, 1μM $ZnCl_2$ (Buffer C). After loading the column is washed in Buffer C and the enzyme is eluted with Buffer C containing 300mM N-Acetyl Glucosamine. The active enzyme fractions are applied to a 1ml Mono Q column equilibrated in Buffer C. After loading and washing with Buffer C, enzyme is eluted using a 0-500mM NaCl gradient in Buffer C. Active enzyme fractions are pooled and used as partially purified proTNFα convertase. In all cases the active fractions are assayed using the fluorogenic synthetic peptide substrate assay described below. This enzyme preparation cleaves 21kD soluble proTNFα at the correct cleavage site (Ala-Val) and enzyme activity is inhibited by matrix metalloprotease inhibitors (Gearing, A.J.H. et al., 1995, J Leukocyte Biol., 57,774-777). 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.Arg.Ser.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH_2 the substrate is used to measure proTNFα convertase enzyme activity in CON2. It was synthesised as follows. The peptidic part of the substrate was assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-fold excess of Fmoc-amino acid and HBTU. Ser^1 and Pro^2 were double-coupled. The following side chain protection strategy was employed; $Ser^1(Bu^t)$, Gln^5(Trityl), $Arg^{8,12}$(Pmc or Pbf), $Ser^{9,10,11}$(Trityl), Cys^{13}(Trityl). Following assembly, the N-terminal Fmoc protecting group was removed by treating the Fmoc-peptidyl-resin with piperidine in DMF. The amino-peptidyl-resin so obtained was acylated by treatment for 1.5-2hr at 70°C with 1.5-2 equivalents of 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid (Khanna & Ullman, Anal Biochem, 108, 156-161, 1980) which had been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF. The dimethoxyfluoresceinyl-peptide was then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and triethylsilane. The dimethoxyfluoresceinyl-peptide was isolated by evaporation, trituration with diethyl ether and filtration. The isolated peptide was reacted with 4-(N-maleimido)-fluorescein in DMF containing diisopropylethylamine, the product purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product was characterised by MALDI-TOF MS and amino acid analysis.

Test compounds are serially diluted in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1% (w/v) Triton X-100 and 2mM $CaCl_2$) and 50μl of each concentration is

added to appropriate wells of a 96 well plate and 50µl assay buffer is added to substrate alone (n=6) and substrate +enzyme (n=6) control wells. ProTNFα convertase enzyme (25µl; 0.0144 units/ml in assay buffer) is added to all wells, except substrate alone controls which receive 25µl assay buffer. (NB: One unit of enzyme activity is defined as the convertase enzyme concentration which converts 1nMole substrate/hour).

Plates are incubated for 15 minutes at 26°C, prior to addition of 25µl substrate (40µM stock solution in assay buffer). Plates are then incubated at 26°C for 18 hours and read on a Fluoroskan II fluorometer (plates are also read at time 0 to obtain background values). In this test, generally, compounds are of interest if they have activity below 500nM. By way of example the compound of Example 1 gave a figure of 1.5 nM.

Assessment in human cell line (THF-2)

The ability of the compounds of this invention to inhibit TNFα production is assessed in THP-1 cells which are a human myelomonocytic cell line which synthesise and secrete TNFα when stimulated with lipopolysaccharide. THP-1 cells ($4x10^5$ cells in 160µl medium RPMI 1640 + bicarbonate, penicillin, streptomycin and glutamine) are incubated with 20µl of test compounds (triplicates) in DMSO or appropriate vehicle, in a 96 well tissue culture (TC) plate, for 30 min at 37°C in a humidified (5%CO_2/95%air) incubator, prior to addition of 20µl lipopolysaccharide (LPS) (E. Coli. 0111:B4 (Sigma); final concentration 50 µg/ml). Each assay includes controls of THP-1 cells incubated with medium alone (six wells/plate) or with a standard TNFα inhibitor. The plates are then incubated for 6 hours at 37°C (humidified incubator) after which time 100µl samples are removed from each well and transferred to a 96 well plate for storage at -70°C for subsequent analysis of TNFα concentration by ELISA. In this test, generally, compounds are of interest if they have activity below 10µM.

Assessment in whole blood assay

The ability of the compounds of this invention to inhibit TNFα production is also assessed in a human whole blood assay (HWBA). Human whole blood secretes TNFα when stimulated with LPS. This property of blood forms the basis of an assay which is used as a secondary test for compounds which profile as active in the THP-1 test. Heparinized (10Units/ml) human blood obtained from volunteers is diluted 1:5 with medium (RPMI1640 + bicarbonate, penicillin, streptomycin and glutamine) and incubated (160µl) with 20µl of

test compound (triplicates), in DMSO or appropriate vehicle, for 30 min at 37°C in a humidified (5%CO_2/95%air) incubator, prior to addition of 20µl LPS (E. coli. 0111:B4; final concentration 10µg/ml). Each assay includes controls of diluted blood incubated with medium alone (6 wells/plate) or a known TNFα inhibitor as standard. The plates are then incubated for 6 hours at 37°C (humidified incubator), centrifuged (2000rpm for 10 min; 4°C), plasma harvested (50-100µl) and stored in 96 well plates at -70°C before subsequent analysis for TNFα concentration by ELISA. In this test, generally, compounds are of interest if they have activity below 50µM.

In vivo assessment

The ability of the compounds of this invention as *ex vivo* TNFα inhibitors is assessed in the rat. Briefly, groups of male Wistar Alderley Park (AP) rats (180-210g) are dosed with compound (6 rats) or drug vehicle (10 rats) by the appropriate route e.g. peroral (p.o.), intraperitoneal (i.p.), subcutaneous (s.c.). Ninety minutes later rats are sacrificed using a rising concentration of CO_2 and bled out via the posterior vena cavae into 5 Units of sodium heparin/ml blood. Blood samples are immediately placed on ice and centrifuged at 2000 rpm for 10 min at 4°C and the harvested plasmas frozen at -20°C for subsequent assay of their effect on TNFα production by LPS-stimulated human blood. The rat plasma samples are thawed and 175µl of each sample are added to a set format pattern in a 96U well plate. Fifty µl of heparinized human blood is then added to each well, mixed and the plate is incubated for 30 min at 37°C (humidified incubator). LPS (25µl; final concentration10µg/ml) is added to the wells and incubation continued for a further 5.5 hours. Control wells are incubated with 25µl of medium alone. Plates are then centrifuged for 10 min at 2000 rpm and 200µl of the supernatants are transferred to a 96 well plate and frozen at -20°C for subsequent analysis of TNF concentration by ELISA.

Data analysis by dedicated software calculates for each compound/dose:

$$\text{Percent inhibition of TNF}\alpha = \frac{\text{Mean TNF}\alpha\text{ (Controls) - Mean TNF}\alpha\text{ (Treated)}}{\text{Mean TNF}\alpha\text{ (Controls)}} \times 100$$

Pharmacokinetic test

To evaluate the clearance properties of the compounds of this invention a sensitive ex vivo pharmacokinetic test is employed which utilises the CON2 assay to evaluate clearance rate.

This is a generic test which can be used to estimate the clearance rate of compounds across a range of species. Animals (eg. rats, marmosets) are dosed iv with a soluble formulation of compound and at subsequent time points (e.g. 5, 10, 15, 20, 30, 45, 60, 120 min) blood samples are taken from an appropriate vessel into 10U heparin. Plasma fractions are obtained following centrifugation and the plasma proteins precipitated with ethanol (70% final concentration). After 30 mins at 4°C the plasma proteins are sedimented by centrifugation and the supernatant fraction is evaporated to dryness using a Savant speed vac. The sediment is reconstituted in CON2 assay buffer and subsequently analysed for compound content using the TNF convertase assay (CON2). Briefly, a compound concentration-response curve is constructed for the compound undergoing evaluation. Serial dilutions of the reconstituted plasma extracts are assessed for activity and the amount of compound present in the original plasma sample is calculated using the concentration-response curve taking into account the total plasma dilution factor.

Test as anti-arthritic agent

Activity of a compound as an anti-arthritic is tested as follows. Acid soluble native type II collagen was shown by Trentham et al. [1] to be arthritogenic in rats; it caused polyarthritis when administered in Freunds incomplete adjuvant. This is now known as collagen-induced arthritis (CIA) and similar conditions can be induced in mice and primates. Recent studies have shown that anti-TNF monoclonal antibodies [2] and TNF receptor-IgG fusion proteins [3] ameliorate established CIA indicating that TNF plays a key role in the pathophysiology of CIA. Moreover, the remarkable efficacy reported for anti-TNF monoclonal antibodies in recent rheumatoid arthritis clinical trials indicates that TNF plays a major role in this chronic inflammatory disease. Thus CIA in DBA/1 mice as described in references 2 and 3 is a tertiary model which can be used to demonstrate the anti-arthritic activity of a compound.

1. Trentham, D.E. et al., (1977) J. Exp. Med., 146, 857.

2. Williams, R.O. et al., (1992) Proc Natl Acad Sci, 89, 9784.

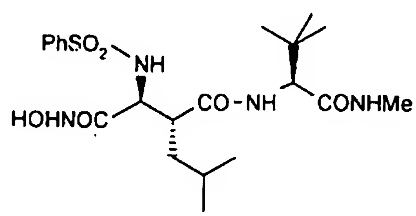
3. Williams, R.O. et al., (1995) Immunology, 84, 433.

In the examples:

(a) NMR spectra were taken at 400 MHz;
(b) DMF means dimethylformamide;
(c) Evaporation of solvents was carried out under reduced pressure;
(d) LDA means lithium di-isopropylamide;
(e) THF means tetrahydrofuran;
(f) DMSO means dimethylsulphoxide;
(g) AcOH means acetic acid;
(h) DMPU means 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone;
(I) DMAP means dimethylaminopyridine.

Example 1

N[2]-[4-(N-Hydroxyamino)-2R-isobutyl-3S-benzenesulfonylaminosuccinyl]-L-tert-leucine-N[1]-methylamide



N[2]-[4-Hydroxy-2R-isobutyl-3S-benzenesulfonylaminosuccinyl]-L-tert-leucine-N[1]-methylamide (600 mg, 1.32 mmol) was dissolved in DMF (10 ml). 1-Hydroxybenzotriazole (231 mg, 1.7 mmol) was added, followed by N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (324 mg, 1.7 mmol) and 2,6-lutidine (181 µl, 1.6 mmol). The mixture was stirred at room temperature for one hour. A solution of hydroxylamine hydrochloride (270 mg, 3.9 mmol) and 2,6-lutidine (453 µl, 3.9 mmol) in DMF (1 ml) was added. The resulting solution was stirred at room temperature for eighteen hours. The resulting mixture was purified by C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 45/55). Elution yielded the title compound (228 mg; yield: 37%); m.p.= 220-222°C; ^{1}H-NMR (DMSO d-6): 0.77 (d, 3H, J= 5.9 Hz), 0.79 (d, 3H, J= 5.9 Hz), 0.91 (s, 9H), 0.92 (m, 1H), 1.31 (m, 1H), 1.47 (m, 1H), 2.59 (d, 3H, J= 4.4 Hz), 2.73 (m, 1H), 3.70 (t br, 1H, J= 9.2 Hz), 4.12 (d, 1H, J= 9.2 Hz), 7.27 (m,

1H), 7.67-7.52 (m, 4H), 7.75 (d, 2H, J= 7.7 Hz), 7.89 (m, 1H), 8.82 (s, 1H), 10.74 (s, 1H); MS (ESI): 493 (M + Na^+).

N^2-[4-Hydroxy-2R-isobutyl-3S-benzenesulfonylaminosuccinyl]-L-tert-leucine-N^1-methylamide used as the starting material was obtained as follows:

(i) To a stirred solution of LDA [75.2 mmol; prepared by addition of 1.6 M n-butyl lithium (47 ml, 75.2 mmol) in hexane to a solution of diisopropylamine (10.53 ml, 80.3 mmol) in dry THF (120 ml) at -78°C] cooled at -78°C under argon atmosphere was added tert-butyl N-(diphenylmethylene)glycinate[(1)] (22.2 g, 75.2 mmol) in dry THF (170 ml) dropwise. The mixture was stirred for 15 minutes at -78°C and DMPU (18 ml, 149 mmol) was added dropwise. The mixture was stirred for 30 minutes at -78°C. A solution of benzyl 2R-trifluoromethanesulfonyloxy-4-methylvalerate[(2)] (26.3 g, 74.2 mmol) in dry THF (170 ml) was added dropwise to the reaction mixture at -78°C. The mixture was stirred at -78°C for one hour and at room temperature for eighteen hours. The solution was diluted in petroleum ether (1000 ml), washed with saturated aqueous ammonium chloride (2 x 600 ml), water (600 ml) and brine (600 ml), dried over $MgSO_4$ and filtered. The solvents were removed and the residue was purified by flash chromatography on silica using petroleum ether-ethyl acetate with 0.5% triethylamine (gradient from 95/5 to 90/10) as eluant to give 1-benzyl-4-tert-butyl-3(R/S)-(N-diphenylmethylene)amino-2R-isobutylbutan-1,4-dioate (36.6 g, R/S 1:3 mixture); ^{1}H-NMR ($CDCl_3$): 0.90-0.81 (m, 6H), 1.39 (s, 9H, 3S isomer), 1.40 (s, 9H, 3R isomer), 1.8-1.1 (m, 3H), 3.22 (m, 1H, 3R isomer), 3.38 (m, 1H, 3S isomer), 4.12 (d, 1H, J= 6.6 Hz, 3S isomer), 4.29 (d, 1H, J= 7 Hz, 3R isomer), 5.03 (d, 1H, J= 12.8 Hz, 3R isomer), 5.07 (d, 1H, J= 12.5 Hz, 3S isomer), 5.10 (d, 1H, J= 12.8 Hz, 3R isomer), 5.16 (d, 1H, J= 12.5 Hz, 3S isomer), 7.7-7.1 (m, 5H).

(1) O'Donnell M.J., Polt R.L.; J. Org. Chem, 1982, 47, 2663

(2) F. Hoffmann La Roche AG, (Broadhurst M.J., Brown P.A., Johnston W.H., Lawton, G.), Eur. Pat. Appl. EP 497192 A2

ii) A solution of 1-benzyl-4-tert-butyl-3(R/S)-(N-diphenylmethylene)amino-2R-isobutylbutan-1,4-dioate (20 g, 40 mmol, R/S 1:3 mixture) in methanol (250 ml) was hydrogenated in the presence of palladium on charcoal (1.5 g, 10%) under 1 bar pressure for 24 hours. The catalyst was removed by filtration and the solvents were removed in vacuo. The yellow solid was triturated with petroleum ether to give 3(R/S)-amino-2R-isobutylbutan-1,4-dioic acid 4-tert-butyl ester (8.07 g, 82%, R/S 1:3 mixture) as a white solid; ^{1}H-NMR (DMSO d-6, CD_3CO_2D): 0.89-0.84 (m, 6H), 1.42 (s, 9H, 3S isomer), 1.44 (s, 9H, 3R isomer), 1.7-1.25 (m, 3H), 2.68 (m, 1H), 3.63 (s br, 1H, 3S isomer), 3.86 (s br, 1H, 3R isomer)

iii) To a slurry of 3(R/S)-amino-2R-isobutylbutan-1,4-dioic acid 4-tert-butyl ester (6.4 g, 26.1 mmol, R/S 1:3 mixture) in dioxane (40 ml) at 0°C was added 1N aqueous sodium hydroxide (58 ml, 58 mmol). The mixture was stirred for five minutes and benzyl chloroformate (5.56 ml, 38.9 mmol) was added dropwise. The mixture was stirred at 0°C for forty five minutes. The mixture was acidified to pH 1 by addition of 2N hydrochloric acid and extracted with ethyl acetate (2x 100 ml). The organic layers were combined, washed with brine (70 ml), dried over $MgSO_4$. The solvents were evaporated in vacuo to give 3(R/S)-benzyloxycarbonylamino-2R-isobutylbutan-1,4-dioic acid 4-tert-butyl ester as a light brown oil which was not purified further. To a solution of 3(R/S)-benzyloxycarbonylamino-2R-isobutylbutan-1,4-dioic acid 4-tert-butyl ester (from above) in dichloromethane (60 ml) at 0°C was added successively 1-hydroxybenzotriazole (4.2 g, 31.2 mmol), L-tert-leucine methyl amide (4.4 g, 30.5 mmol), DMAP (4.2 g, 34.4 mmol) and N-ethyl-N'-(3-dimethylamino-propyl)carbodiimide hydrochloride (6 g, 31.4 mmol). The mixture was stirred at room temperature for eighteen hours. The solvents were evaporated in vacuo. The residue was partitionned between 2N hydrochloric acid (200 ml) and ethyl acetate (2 x 150 ml). The combined organic layers were washed with saturated sodium bicarbonate, brine, dried over $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by flash chromatography on silica using ether-petroleum ether (65:35) as eluent to give N^2-[2R-isobutyl-3S-benzyloxycarbonylamino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (8.0 g, 61%) as a white foam; ^{1}H-NMR ($CDCl_3$): 0.90 (d, 6H, J= 5.5 Hz), 0.96 (s, 9H), 1.42 (s, 9H), 1.7-1.35 (m, 3H), 2.80 (d, 1H, J= 4.8 Hz), 2.95 (m, 1H), 4.09 (d, 1H, J=

9.2 Hz), 4.35 (dd, 1H, J= 9.2 Hz, J'= 3.3 Hz), 5.13 (s, 2H), 5.66 (s br, 1H), 6.31 (d br, 1H, J= 6.9 Hz), 7.35-7.25 (m, 5H).

iv) A solution of N^2-[2R-isobutyl-3S-benzyloxycarbonylamino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (3.5 g, 6.9 mmol) in methanol (50 ml) was hydrogenated under 28 PSI pressure for two hours in the presence of palladium on charcoal (700 mg, 10%). The catalyst was removed by filtration and the solvents were removed in vacuo to give N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (2.57 g, 100%) as a white solid. ^1H-NMR ($CDCl_3$): 0.91 (d, 3H, J= 6.6 Hz), 0.96 (d, 3H, J= 6.6 Hz), 1.01 (s, 9H), 1.46 (s, 9H), 1.7-1.3 (m, 3H), 2.75 (m, 1H), 2.76 (d, 1H, J= 4.7 Hz), 3.59 (s br, 1H), 4.14 (d, 1H, J= 8.8 Hz), 6.15 (m, 1H), 7.97 (d br, 1H, J= 9.2 Hz).

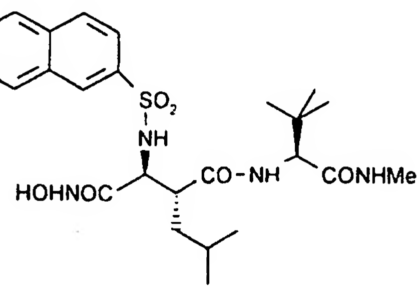
v) To a solution of N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (740 mg, 1.98 mmol) in dichloromethane (10 ml) at 0°C was added successively pyridine (500 μl, 6.18 mmol), benzenesulfonyl chloride (310 μl, 2.43 mmol) and DMAP (a few crystals). The mixture was stirred at room temperature for eighteen hours. The reaction mixture was poured into 2N hydrochloric acid (50 ml) and extracted with ethyl acetate (2 x 60 ml). The combined organic layers were washed with brine, dried over $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by flash chromatography on silica using ethyl acetate-petroleum ether (1:1) as eluant to give N^2-[2R-isobutyl-3S-benzenesulfonylamino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (849 mg, 84%) as a white foam. ^1H-NMR ($CDCl_3$): 0.88 (d, 3H, J= 6.6 Hz), 0.89 (d, 3H, J= 6.6 Hz), 0.96 (s, 9H), 1.23 (s, 9H), 1.65-1.40 (m, 3H), 2.82 (d, 3H, J= 4.7 Hz), 3.98 (dd, 1H, J= 9.9 Hz, J= 3.3 Hz), 4.08 (d, 1H, J= 9.1 Hz), 5.75 (s br, 1H), 6.26 (d br, 1H, J= 8.8 Hz), 6.37 (d br, 1H, J= 9.9 Hz), 7.55-7.45 (m, 3H), 7.86 (d, 2H, J= 7 Hz).

vi) Trifluoroacetic acid (2 ml) was added dropwise to a solution of N^2-[2R-isobutyl-3S-benzenesulfonylamino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (780 mg, 1.52 mmol) in dry dichloromethane (4 ml). The solution was stirred at 0°C overnight. The solvents were evaporated in vacuo. The residue was taken up in toluene and the solvent was removed in vacuo (three times). The residue was triturated in a mixture of pentane and ether to give

white crystals which were collected and dried in vacuo to yield N^2-[4-hydroxy-2R-isobutyl-3S-benzenesulfonylaminosuccinyl]-L-tert-leucine-N^1-methylamide (676 mg, 98%)
MS (ESI): 456 (M + H^+), 478 (M + Na^+).

Example 2

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(naphthalene-2-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide



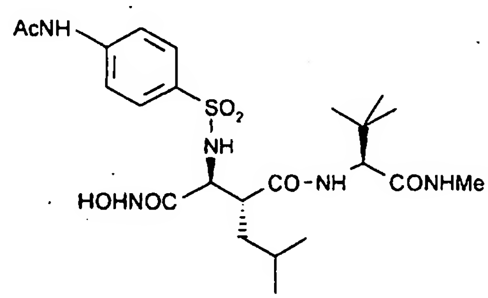
In a manner analogous to that described in the first paragraph of Example 1 except that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)-hydroxylamine (191 mg, 1.30 mmol), from N^2-[4-hydroxy-2R-isobutyl-3S-(naphthalene-2-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (480 mg, 0.95 mmol) there was obtained the title compound (362 mg, 73%) as a white solid after addition of 1 ml of 1N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 60/40); m.p.= 214-216°C; ^{1}H-NMR (DMSO d-6): 0.75 (d, 3H, J= 7 Hz), 0.77 (d, 3H, J= 7 Hz), 0.90 (s, 9H), 0.92 (m, 1H), 1.30 (m, 1H), 1.46 (m, 1H), 2.60 (d, 3H, J= 4.4 Hz), 2.75 (m, 1H), 3.76 (m, 1H), 4.13 (d, 1H, J= 9.2 Hz), 7.27 (m, 1H), 7.78-7.68 (m, 4H), 7.89 (m, 1H), 8.14-8.06 (m, 3H), 8.39 (s, 1H), 8.79 (s, 1H), 10.79 (s, 1H); MS (ESI): 543 (M + Na^+).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v) , from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (600 mg, 1.6 mmol) and naphthalene-2-sulfonyl chloride (403 mg), there was obtained N^2-[2R-isobutyl-3S-(naphthalene-2-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (690 mg, 77%) as a white foam; MS (ESI): 584 (M + Na^+). This (650

mg, 1.15 mmol), in a manner analogous to that described in Example 1 (vi), was converted to N²-[4-hydroxy-2R-isobutyl-3S-(naphthalene-2-sulfonylamino)succinyl]-L-tert-leucine-N¹-methylamide (540 mg, 93%) as a white solid. MS (ESI): 506 (M + H⁺), 528 (M + Na⁺).

Example 3

N²-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-acetamidobenzenesulfonylamino)succinyl]-L-tert-leucine-N¹-methylamide.



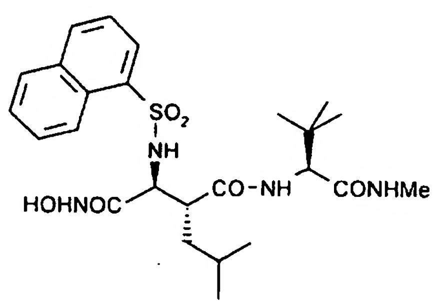
In a manner analogous to that described in the first paragraph of Example 1, from N²-[4-hydroxy-2R-isobutyl-3S-(4-acetamidobenzenesulfonylamino)succinyl]-L-tert-leucine-N¹-methylamide (512 mg, 1 mmol), except that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)hydroxylamine (191 mg, 1.30 mmol), there was obtained the title compound (335 mg, 63%) as a white solid after addition of 1 ml of 1N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 40/60); m.p.= 272-274°C; ¹H-NMR (DMSO d-6): 0.79 (d, 3H, J= 6.2 Hz), 0.80 (d, 3H, J= 6.2 Hz), 0.95 (s, 9H), 0.96 (m, 1H), 1.32 (m, 1H), 1.49 (m, 1H), 2.15 (s, 3H), 2.61 (d, 3H, J= 4.4 Hz), 2.72 (m, 1H), 3.67 (m, 1H), 4.16 (d, 1H, J= 9.2 Hz), 7.28 (d, 1H, J= 9.5 Hz), 7.47 (m, 1H), 7.67 (d, 2H, J= 8.8 Hz), 7.73 (d, 2H, J= 8.8 Hz), 7.90 (m, 1H), 8.83 (s, 1H), 10.31 (s, 1H), 10.73 (s, 1H); MS (ESI): 550 (M + Na⁺).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v), from N²-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N¹-methylamide (600 mg, 1.6 mmol) and 4-acetamidobenzenesulfonyl chloride (415 mg), there

was obtained N^2-[2R-isobutyl-3S-(4-acetamidobenzenesulfonylamino)-4-tert-butyloxy-succinyl]-L-tert-leucine-N^1-methylamide (790 mg, 87%) as a white foam; MS (ESI): 591 (M + Na^+). This (750 mg, 1.32 mmol), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(4-acetamidobenzenesulfonylamino)-succinyl]-L-tert-leucine-N^1-methylamide (656 mg, 97%) as a white solid; MS (ESI): 513 (M + H^+), 535 (M + Na^+).

Example 4

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(naphthalene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide

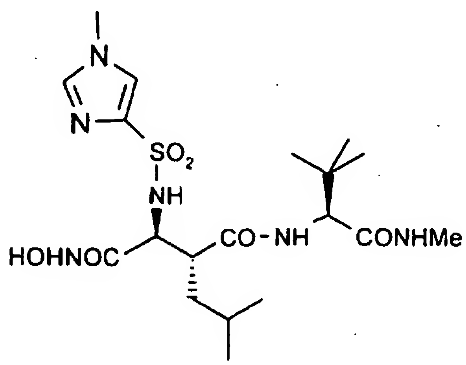


In a manner analogous to that described in the first paragraph of Example 1, from N^2-[4-hydroxy-2R-isobutyl-3S-(naphthalene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1 mmol), except that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)hydroxylamine (191 mg, 1.30 mmol), there was obtained the title compound (342 mg, 62%) as a white solid after addition of 1 ml of 1N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 55/45); m.p.= 162-170°C; ^{1}H-NMR (DMSO d-6): 0.65 (d, 3H, J= 5.9 Hz), 0.70 (d, 3H, J= 6.2 Hz), 0.91 (m, 1H), 0.92 (s, 9H), 1.20 (m, 1H), 1.35 (m, 1H), 2.60 (d, 3H, J= 4.4 Hz), 2.75 (m, 1H), 3.72 (d br, 1H, J= 8.8 Hz), 4.16 (d, 1H, J= 9.2 Hz), 7.45 (m, 1H), 7.80-7.55 (m, 4H), 7.92 (s br, 1H), 8.25-8.05 (m, 3H), 8.67-8.57 (m, 2H), 10.79 (s, 1H); MS (ESI): 543 (M + Na^+).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v), from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (600 mg, 1.6 mmol) and naphthalene-1-sulfonyl chloride (403 mg), there was obtained N^2-[2R-isobutyl-3S-(naphthalene-1-sulfonylamino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (620 mg, 69%) as a white foam; MS (ESI): 584 (M + Na^+). This (600 mg, 1.06 mmol), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(naphthalene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (518 mg, 96%) as a white solid. MS (ESI): 506 (M + H^+), 528 (M + Na^+).

Example 5

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(1-methylimidazole-4-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide



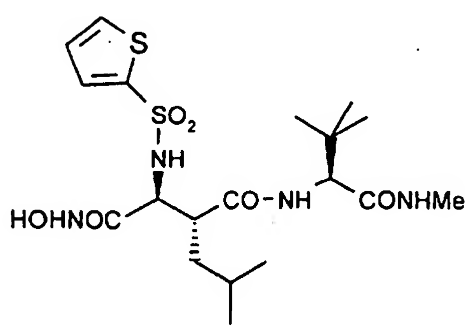
In a manner analogous to that described in the first paragraph of Example 1, except that 2.6 equivalents of 1-hydroxybenzotriazole, 2.6 equivalents of N-ethyl-N'-(3-dimethylamino-propyl)carbodiimide hydrochloride and 2.6 equivalents of 2,6-lutidine were used and hydroxylamine hydrochloride was replaced by O-(tert-butyldimethylsilyl)hydroxylamine (538 mg, 3 eq.), from N^2-[4-hydroxy-2R-isobutyl-3S-(1-methylimidazolium-4-sulfonylamino)-succinyl]-L-tert-leucine-N^1-methylamide trifluoroacetate salt (700 mg, 1.22 mmol), there was obtained the title compound (265 mg, 46%) as a white solid after addition of water (2 ml) and acetic acid (1 ml) to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 40/60), ^{1}H-NMR (DMSO d-6): 0.75 (d, 3H, J= 6.2 Hz), 0.76 (d, 3H,

J= 6.2 Hz), 0.90 (m, 1H), 0.92 (s, 9H), 1.29 (m, 1H), 1.41 (m, 1H), 2.56 (d, 3H, J= 4.4 Hz), 2.75 (m, 1H), 3.62 (t, 1H, J= 8.8 Hz), 3.67 (s, 3H), 4.14 (d, 1H, J= 9.1 Hz), 7.17 (d, 1H, J= 9.1 Hz), 7.41 (d, 1H, J= 9.2 Hz), 7.51 (s, 1H), 7.70 (s, 1H), 7.84 (m, 1H), 8.74 (s, 1H), 10.59 (s, 1H); MS (ESI): 497 ($M + Na^+$).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v) except that the crude reaction mixture after evaporation of the solvents was directly purified by flash chromatography on silica using dichloromethane-methanol (95:5) as eluant, from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (700 mg, 1.88 mmol) and 1-methyl-imidazole-4-sulfonyl chloride (375 mg), there was obtained N^2-[2R-isobutyl-3S-(1-methylimidazole-4-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (953 mg, 98%) as a white foam. MS (ESI): 516 ($M + H^+$). This (900 mg, 1.74 mmol), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(1-methylimidazolium-4-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide trifluoroacetate salt (819 mg) as a white solid. MS (ESI): 460 ($M-CF_3COOH + H^+$).

Example 6

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophene-2-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide



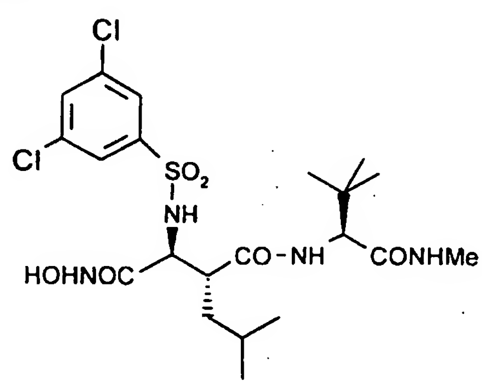
In a manner analogous to that described in the first paragraph of Example 1, except that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)-hydroxylamine (191 mg, 1.30 mmol), from N^2-[4-hydroxy-2R-isobutyl-3S-(thiophene-2-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (400 mg, 0.86 mmol), there was obtained the title compound (245 mg, 60%) as a white solid after addition of 1 ml of 1N

hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 40/60); ^{1}H-NMR (DMSO d-6): 0.75 (d, 3H, J= 6.2 Hz), 0.76 (d, 3H, J= 6.2 Hz), 0.91 (s, 9H), 0.93 (m, 1H), 1.29 (m, 1H), 1.46 (m, 1H), 2.56 (d, 3H, J= 4.4 Hz), 2.71 (m, 1H), 3.69 (d, 1H, J= 9.9 Hz), 4.12 (d, 1H, J= 9.1 Hz), 7.10 (t, 1H, J= 4.0 Hz), 7.23 (m, 1H), 7.47 (d, 1H, J= 4.0 Hz), 7.79 (m, 1H), 7.86 (m, 2H), 8.84 (s, 1H), 10.75 (s, 1H); MS (ESI): 499 (M + Na$^+$).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v), from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1.34 mmol) and thiophene-2-sulfonyl chloride (295 mg), there was obtained N^2-[2R-isobutyl 3S-(thiophene-2-sulfonylamino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (567 mg, 82%) as a white foam; MS (ESI): 540 (M + Na$^+$). This (600 mg, 1.06 mmol), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy 2R-isobutyl 3S-(thiophene-2-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (518 mg, 96%) as a white solid. MS (ESI): 462 (M + H$^+$), 484 (M + Na$^+$).

Example 7

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3,5-dichlorobenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide



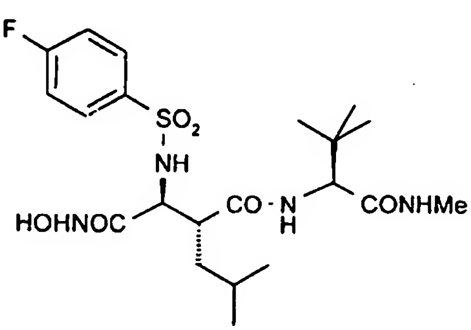
In a manner analogous to that described in the first paragraph of Example 1, except that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)hydroxylamine (191 mg, 1.30 mmol), from N^2-[4-hydroxy-2R-isobutyl-3S-(3,5-

dichlorobenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (450 mg, 0.85 mmol), there was obtained the title compound (310 mg, 68%) as a white solid after addition of 2 ml of 2N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/ 1%AcOH (gradient from 0/100 to 40/60); ^{1}H-NMR (DMSO d-6): 0.75 (d, 3H, J= 6.6 Hz), 0.76 (d, 3H, J= 6.6 Hz), 0.89 (s, 9H), 0.95 (m, 1H), 1.29 (m, 1H), 1.43 (m, 1H), 2.56 (d, 3H, J= 4.4 Hz), 2.67 (m, 1H), 3.65 (t, 1H, J= 9.5 Hz), 4.12 (d, 1H, J= 9.5 Hz), 7.17 (d, 1H, J= 9.5 Hz), 7.67 (s, 2H), 7.88 (m, 2H), 8.12 (d, 1H, J= 9.5 Hz), 8.86 (s, 1H), 10.79 (s, 1H); MS (ESI): 563 (M{^{35}Cl, ^{37}Cl} + Na$^+$), 561 (M{^{35}Cl, ^{35}Cl} + Na$^+$).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v), from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1.34 mmol) and 3,5-dichlorobenzenesulfonyl chloride (500 mg), there was obtained N^2-[2R-isobutyl-3S-(3,5-dichlorobenzene-1-sulfonylamino-4-tert-butyloxy-succinyl]-L-tert-leucine-N^1-methylamide (629 mg, 81%) as a white foam. MS (ESI): 604 (M{^{37}Cl, ^{35}Cl} + Na$^+$), 602 (M{^{35}Cl, ^{35}Cl} + Na$^+$). This (580 mg, 1.0 mmol) in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(3,5-dichlorobenzene-1-sulfonylaminosuccinyl]-L-tert-leucine-N^1-methylamide (480 mg, 92%) as a white solid. MS (ESI): 548 (M{^{37}Cl, ^{35}Cl} + Na$^+$), 546 (M{^{35}Cl, ^{35}Cl} + Na$^+$)

Example 8

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-fluorobenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide



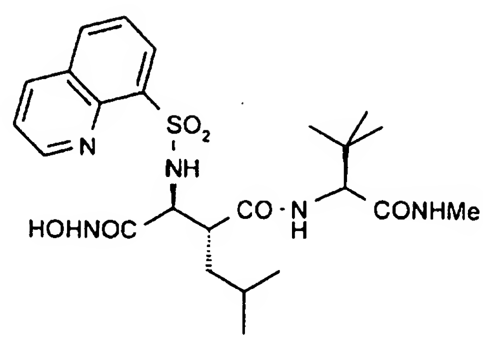
In a manner analogous to that described in the first paragraph of Example 1, except that hydroxylamine hydrochloride was replaced by O-(tert-butyldimethylsilyl)hydroxylamine (186

mg, 1.27 mmol) and 2,6-lutidine (138 µl, 1.26 mmol) was added, from N^2-[4-hydroxy-2R-isobutyl-3S-(4-fluorobenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (400 mg, 0.86 mmol), there was obtained N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-fluoro-benzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (262 mg, 64%) as a white solid after addition of 3 ml of 2N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 50/50); ^{1}H-NMR (DMSO d-6): 0.74 (d, 3H, J= 6.2 Hz), 0.76 (d, 3H, J= 6.2 Hz), 0.89 (s, 9H), 0.90 (m, 1H), 1.29 (m, 1H), 1.44 (m, 1H), 2.57 (d, 3H, J= 4.4 Hz), 2.68 (m, 1H), 3.65 (m, 1H), 4.11 (d, 1H, J= 9.2 Hz), 7.22 (d, 1H, J= 9.2 Hz), 7.34 (dd, 2H, J=J'= 8.8 Hz), 7.65 (m, 1H), 7.76 (dd, 2H, J= 8.8 Hz, J'= 5.5 Hz), 7.87 (m, 1H), 8.74 (s, 1H), 10.70 (s, 1H); MS (ESI): 511 ($M + Na^+$).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v), from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1.34 mmol) and 4-fluorobenzenesulfonyl chloride (393 mg, 2 mmol), there was obtained N^2-[2R-isobutyl-3S-(4-fluorobenzene-1-sulfonylamino-4-tert-butyloxy-succinyl]-L-tert-leucine-N^1-methylamide (522 mg, 74%) as a white foam: MS (ESI): 552 ($M + Na^+$). This (500 mg, 0.94 mmol), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(4-fluorobenzene-1-sulfonylamino)-succinyl]-L-tert-leucine-N^1-methylamide (448 mg, 100%) as a white solid. MS (ESI): 474 ($M + H^+$).

Example 9

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide

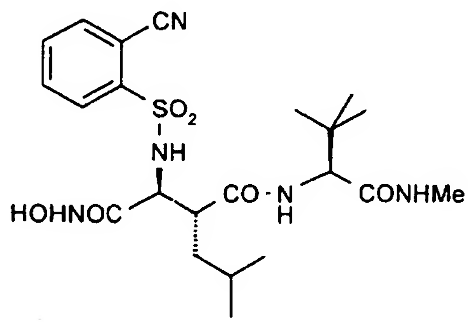


In a manner analogous to that described in the first paragraph of Example 1, except that hydroxylamine hydrochloride was replaced by O-(tert-butyldimethylsilyl)hydroxylamine (130 mg, 0.88 mmol) and 2,6-lutidine (97 µl, 0.88 mmol) was added, from N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (300 mg, 0.59 mmol), there was obtained the title compound (190 mg, 59%) as a white solid after addition of 3 ml of 2N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 40/60): ^{1}H-NMR (DMSO d-6): 0.62 (d, 3H, J= 6.6 Hz), 0.65 (d, 3H, J= 6.6 Hz), 0.82 (m, 1H), 0.86 (s, 9H), 1.3-1.0 (m, 2H), 2.56 (d, 3H, J= 4.8 Hz), 2.83 (m, 1H), 3.84 (m, 1H), 4.15 (d, 1H, J= 9.2 Hz), 7.39 (m, 1H), 7.83-7.68 (m, 4H), 8.25-8.19 (m, 2H), 8.53-8.44 (m, 2H), 9.06 (m, 1H), 10.47 (m, 1H); MS (ESI): 522 (M + H^+), 544 (M + Na^+).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v), from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1.34 mmol) and 8-quinolinesulfonyl chloride (460 mg, 2.02 mmol), there was obtained N^2-[2R-isobutyl-3S-(quinoline-8-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (375 mg, 50%) as a white foam. MS (ESI): 563 (M + Na^+). This (350 mg, 0.62 mmol), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (315 mg, 100%) as a white solid. MS (ESI): 507 (M + H^+).

Example 10

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-cyanobenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide

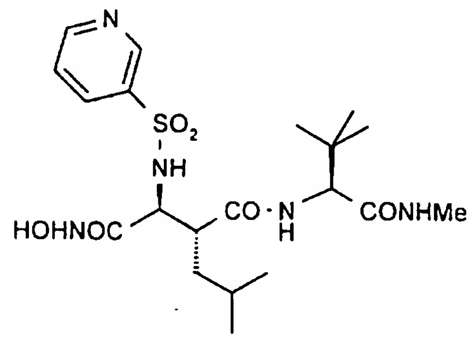


In a manner analogous to that described in the first paragraph of Example 1, except that hydroxylamine hydrochloride, 2,6-lutidine, 1-hydroxybenzotriazole and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride and DMF were replaced by O-(tert-butyldimethylsilyl)hydroxylamine (175 mg, 1.19 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (254 mg, 1.03 mmol) and chloroform, from N^2-[4-hydroxy-2R-isobutyl-3S-(2-cyanobenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (380 mg, 0.79 mmol), there was obtained the title compound (202 mg, 52%) as a white solid after evaporation of the solvents, partitioning between ether and water, and filtration of the resulting solid. ^{1}H-NMR (DMSO d-6): 0.75 (d, 3H, J= 6.0 Hz), 0.77 (d, 3H, J= 6.0 Hz), 0.91 (m, 1H), 0.93 (s, 9H), 1.30 (m, 1H), 1.46 (m, 1H), 2.58 (d, 3H, J= 4.4 Hz), 2.84 (m, 1H), 3.67 (dd, 1H, J=J'= 9.6 Hz), 4.18 (d, 1H, J= 9.2 Hz), 7.56 (d, 1H, J= 9.2 Hz), 8.04-7.76 (m, 6H), 8.67 (s, 1H), 10.57 (s, 1H); MS (ESI): 518 (M + Na$^+$).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v), from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1.34 mmol) and 2-cyanobenzenesulfonyl chloride (407 mg, 2.02 mmol), there was obtained N^2-[2R-isobutyl-3S-(2-cyanobenzene-1-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (507 mg, 71%) as a white foam; MS (ESI): 559 (M + Na$^+$). This (480 mg) in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(2-cyanobenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (400 mg, 93%) as a white solid. MS (ESI): 481 (M + H$^+$), 503 (M + Na$^+$).

Example 11

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-pyridinesulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide

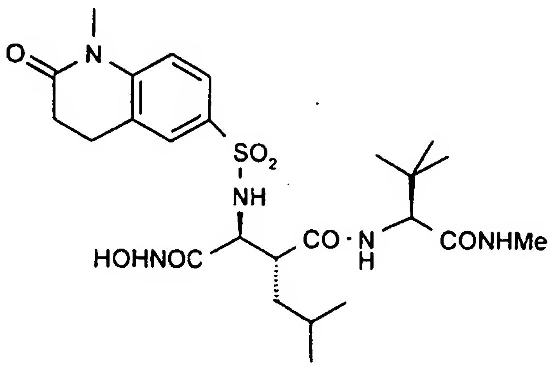


In a manner analogous to that described in the first paragraph of Example 1, except that hydroxylamine hydrochloride was replaced by O-(tert-butyldimethylsilyl)hydroxylamine (205 mg) and 2,6-lutidine (153 μl) was used, from N^2-[4-hydroxy-2R-isobutyl-3S-(3-pyridine-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (320 mg, 0.7 mmol), there was obtained the title compound (315 mg, 94%) as a white solid after addition of 2 ml of 2N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 35/65); m.p.= 228-231°C; ^{1}H-NMR (DMSO d-6): 0.75 (d, 3H, J= 6.6 Hz), 0.76 (d, 3H, J= 6.6 Hz), 0.88 (s, 9H), 0.90 (m, 1H), 1.29 (m, 1H), 1.44 (m, 1H), 2.56 (d, 3H, J= 4.8 Hz), 2.68 (m, 1H), 3.69 (d br. 1H, J= 9.9 Hz), 4.10 (d, 1H, J= 9.5 Hz), 7.20 (m, 1H), 7.56 (dd, 1H, J= 4.8 Hz, J'= 8 Hz), 7.87 (m, 1H), 7.96 (m, 1H), 8.04 (d, 1H, J= 8 Hz), 8.76 (d, 1H, J= 4.8 Hz), 8.81 (m, 1H), 8.86 (s, 1H), 10.75 (m, 1H); MS (ESI): 494 (M + Na^+).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v), from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1.34 mmol) and 3-pyridinesulfonyl chloride (360 mg), there was obtained N^2-[2R-isobutyl-3S-(3-pyridinesulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (500 mg, 73%) as a white foam; MS (ESI): 513 (M + H^+), 535 (M + Na^+). This (470 mg, 0.92 mmol), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(3-pyridinesulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (340 mg) as a white solid; MS (ESI): 457 (M + H^+), 479 (M + Na^+).

Example 12

N[2]-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-sulfonylamino)succinyl]-L-tert-leucine-N[1]-methylamide



In a manner analogous to that described in the first paragraph of Example 1. except that hydroxylamine hydrochloride was replaced by O-(tert-butyldimethylsilyl)hydroxylamine (273 mg) and 2,6-lutidine (202 μl) was used, from N[2]-[4-hydroxy-2R-isobutyl-3S-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-sulfonylamino)succinyl]-L-tert-leucine-N[1]-methylamide (500 mg, 0.92 mmol), there was obtained N2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-sulfonylamino)succinyl]-L-tert-leucine-N1-methylamide (322 mg, 63%) as a white solid after addition of 2 ml of 4N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 50/50). m.p.= 260-262°C; ^{1}H-NMR (DMSO d-6): 0.74 (d, 3H, J= 6.6 Hz), 0.76 (d, 3H, J= 6.6 Hz), 0.90 (m, 1H), 0.91 (s, 9H), 1.28 (m, 1H), 1.44 (m, 1H), 2.56 (d, 3H, J= 4.4 Hz), 2.59 (m, 2H), 2.69 (m, 1H), 2.92 (m, 2H), 3.29 (s, 3H), 3.63 (m, 1H), 4.12 (d, 1H, J= 9.1 Hz), 7.17 (d, 1H, J= 8.4 Hz), 7.25 (d, 1H, J= 8.8 Hz), 7.42 (m, 1H), 7.57 (m, 2H), 7.85 (m, 1H), 8.76 (s, 1H), 10.72 (s, 1H); MS (ESI): 576 (M + Na^+).

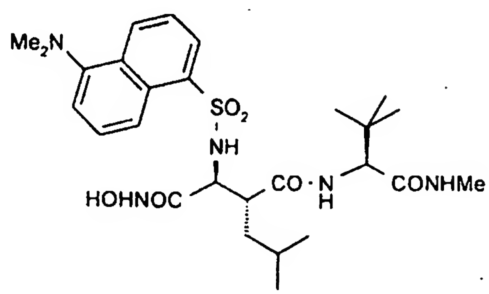
The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v), from N[2]-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N[1]-methylamide (500 mg, 1.34 mmol) and 1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-sulfonyl chloride[(note)] (524 mg), there was obtained N[2]-[2R-isobutyl-3S-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N[1]-methylamide (679 mg, 85%) as a white foam; MS (ESI): 617 (M + Na^+). This (650 mg, 1.09 mmol) in a

manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (520 mg, 88%) as a white solid. MS (ESI): 539 (M + H⁺), 561 (M + Na⁺).

(note) Imperial Chemical Industries PLC, ICI-Pharma S.A.; (Bruneau, P.); Eur. Pat. Appl. EP 462812 A2

Example 13

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(5-dimethylaminonaphthalene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide

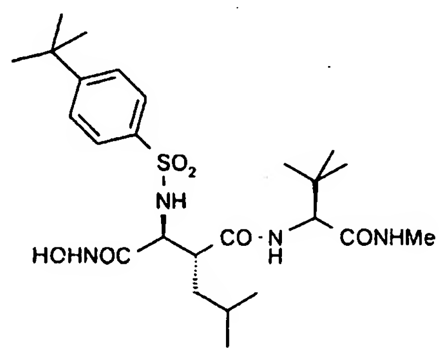


In a manner analogous to that described in the first paragraph of Example 1, except that no 1-hydroxybenzotriazole was added and that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)hydroxylamine (262 mg), from N^2-[4-hydroxy-2R-isobutyl-3S-(5-dimethylaminonaphthalene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (490 mg, 0.89 mmol), there was obtained the title compound (270 mg, 54%) as a solid after addition of 2 ml of acetic acid, methanol (20 ml) and water (10 ml) to the crude mixture at the end of the reaction, stirring overnight and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 60/40). m.p.= 170-174°C; ^{1}H-NMR (DMSO d-6): 0.62 (d, 3H, J= 6.2 Hz), 0.66 (d, 3H, J= 6.2 Hz), 0.87 (s, 9H), 0.90 (m, 1H), 1.17 (m, 1H), 1.32 (m, 1H), 2.56 (d, 3H, J= 4.8 Hz), 2.74 (m, 1H), 2.84 (s, 6H), 3.69 (m, 1H), 4.13 (d, 1H, J= 8.8 Hz), 7.25 (d, 1H, J= 7.7 Hz), 7.44 (m, 1H), 7.57 (m, 2H), 7.77 (m, 1H), 7.88 (m, 1H), 8.07 (d, 1H, J= 7 Hz), 8.19 (d, 1H, J= 8.4 Hz), 8.43 (d, 1H, J= 8.4 Hz), 8.66 (s, 1H), 10.6 (s, 1H); MS (ESI): 586 (M + Na⁺).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v) except that after completion of the reaction the mixture was diluted with ethyl acetate, washed with 5% sodium bicarbonate and purified by flash chromatography on silica gel, from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1.34 mmol) and dansyl chloride (473 mg), there was obtained N^2-[2R-isobutyl-3S-(5-dimethylaminonaphthalene-1-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (660 mg, 81%) as a foam. MS (ESI): 627 (M + Na^+). This (630 mg, 1.04 mmol), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(5-dimethylaminonaphthalene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (518 mg, 91%) as a solid. MS (ESI): 549 (M + H^+).

Example 14

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tert-butylbenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide



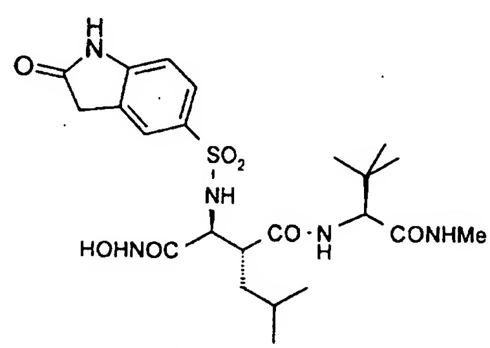
In a manner analogous to that described in the first paragraph of Example 1, except that no 1-hydroxybenzotriazole was added and that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)hydroxylamine (167 mg), from N^2-[4-hydroxy-2R-isobutyl-3S-(4-tert-butylbenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (387 mg, 0.75 mmol), there was obtained the title compound (272 mg, 70%) as a white solid after addition of 2 ml of 4N hydrochloric acid, water (20 ml) and petroleum ether (20 ml) to the crude mixture at the end of the reaction, filtration and washing of the white solid with petroleum ether. m.p.= 170-172°C; ^{1}H-NMR (DMSO d-6): 0.75 (d, 3H, J= 6.2 Hz), 0.76 (d, 3H, J= 6.2 Hz), 0.85 (s, 9H), 0.87 (m, 1H), 1.33 (s, 9H), 1.40-1.20 (m, 2H), 2.57 (d, 3H, J= 4.4

Hz), 2.73 (m, 1H), 3.69 (m, 1H), 4.10 (d, 1H, J= 9.1 Hz), 7.27 (d, 1H, J= 8.8 Hz), 7.48 (d, 1H, J= 9.1 Hz), 7.54 (d, 2H, J= 8.4 Hz), 7.66 (d, 2H, J= 8.4 Hz), 7.87 (m, 1H), 8.85 (s, 1H), 10.71 (s, 1H); MS (ESI): 549 (M + Na^+).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v), from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1.34 mmol) and 4-tert-butylbenzene sulfonyl chloride (410 mg), there was obtained N^2-[2R-isobutyl-3S-(4-tert-butylbenzene-1-sulfonylamino)-4-tert-butyloxy-succinyl]-L-tert-leucine-N^1-methylamide (660 mg) as a white foam. MS (ESI): 590 (M + Na^+). This (630 mg), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(4-tert-butylbenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (407 mg) as a white solid; MS (ESI): 512 (M + H^+).

Example 15

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(oxindole-5-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide



In a manner analogous to that described in the first paragraph of Example 1, except that no 1-hydroxybenzotriazole was added and that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)hydroxylamine (203 mg), from N^2-[4-hydroxy-2R-isobutyl-3S-(oxindole-5-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (470 mg, 0.92 mmol), there was obtained the title compound (228 mg, 47%) as a white solid after addition of 2 ml of 4N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 45/55). m.p.= 232-234°C; ^{1}H-NMR (DMSO d-6):

0.73 (d, 3H, J= 6.6 Hz), 0.74 (d, 3H, J= 6.6 Hz), 0.85 (m, 1H), 0.90 (s, 9H), 1.27 (m, 1H), 1.41 (m, 1H), 2.56 (d, 3H, J= 4.8 Hz), 2.68 (m, 1H), 3.53 (s, 2H), 3.59 (m, 1H), 4.11 (d, 1H, J= 9.1 Hz), 6.86 (d, 1H, J= 8 Hz), 7.25 (m, 1H), 7.32 (m, 1H), 7.52 (s, 1H), 7.55 (d, 1H, J= 8 Hz), 7.85 (m, 1H), 8.76 (s, 1H), 10.69 (s, 1H), 10.75 (s, 1H): MS (ESI): 548 ($M + Na^+$).

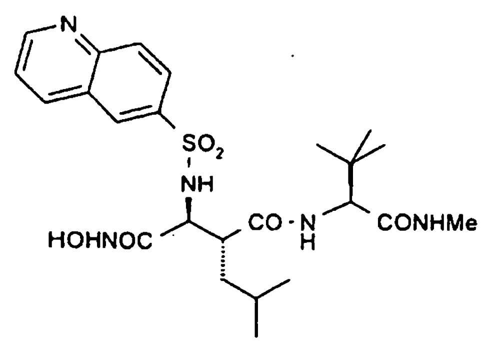
The starting material was prepared as follows:

(i) In a manner analogous to that described in Example 1 (v), from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1.34 mmol) and oxindole-5-sulfonyl chloride [(Note)] (405 mg), there was obtained N^2-[2R-isobutyl-3S-(oxindole-5-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (660 mg) as a white foam. MS (ESI): 589 ($M + Na^+$). This (630 mg), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(oxindole-5-sulfonylamino)-succinyl]-L-tert-leucine-N^1-methylamide (496 mg) as a solid. MS (ESI): 533 ($M + Na^+$).

[(Note)] Prepared by reaction of oxindole with chlorosulfonic acid.

Example 16

N^2-[4-(N-Hydroxyamino) 2R-isobutyl 3S-(quinoline 6-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide



In a manner analogous to that described in the first paragraph of Example 1, except that no 1-hydroxybenzotriazole was added and that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)hydroxylamine (352 mg), from N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-6-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (500 mg), there was obtained the title compound (204 mg) as a white solid after addition of 2 ml of 2N

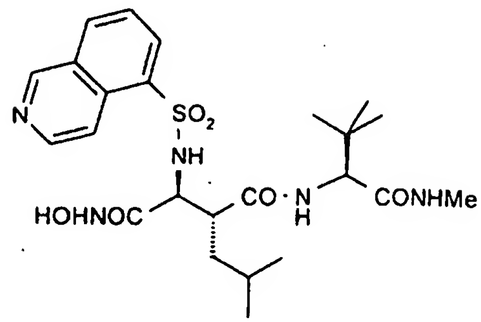
hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 50/50). m.p.= 248-250°C; ^{1}H-NMR (DMSO d-6): 0.72 (d, 3H, J= 7 Hz), 0.74 (d, 3H, J= 7 Hz), 0.85 (s, 9H), 0.89 (m, 1H), 1.27 (m, 1H), 1.45 (m, 1H), 2.56 (d, 3H, J= 4.4 Hz), 2.70 (m, 1H), 3.73 (m, 1H), 4.11 (d, 1H, J= 9.1 Hz), 7.22 (d, 1H, J= 9.1 Hz), 7.68 (m, 1H), 7.83 (m, 2H), 7.97 (d, 1H, J= 9.1 Hz), 8.12 (d, 1H, J= 9.1 Hz), 8.43 (s, 1H), 8.54 (d, 1H, J= 9.1 Hz), 8.74 (s, 1H), 9.05 (m, 1H), 10.76 (s, 1H);.MS (ESI): 522 (M + H$^+$).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v) except that the reaction mixture was directly purified by flash chromatography on silica gel after evaporation of the solvents, from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxy-succinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1.34 mmol) and quinoline-6-sulfonyl chloride [(Note)] (400 mg), there was obtained N^2-[2R-isobutyl-3S-(quinoline 6-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (510 mg, 67%) as a white foam. MS (ESI): 563 (M + H$^+$). This (490 mg), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-6-sulfonyl-amino)succinyl]-L-tert-leucine-N^1-methylamide (530 mg) as a white solid. MS (ESI): 507 (M + H$^+$).

[(Note)] Quinoline 6-sulfonyl chloride was prepared in two steps: preparation of quinoline-6-sulfonic acid from sulfanilic acid (Ponci R, Gialdi, F; Chem. Abstracts, 1955, 49,11657b) followed by reaction of quinoline-6-sulfonic acid with phosphorus pentachloride.

Example 17

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(isoquinoline-5-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide

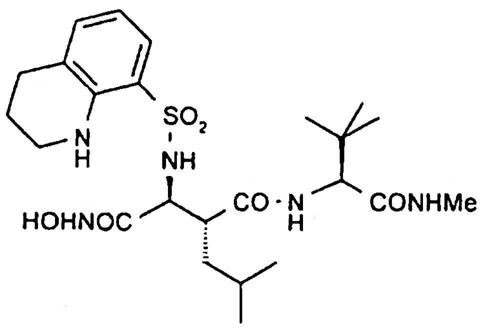


In a manner analogous to that described in the first paragraph of Example 1, except that no 1-hydroxybenzotriazole was added and that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)hydroxylamine (250 mg), from N^2-[4-hydroxy-2R-isobutyl-3S-(isoquinoline-5-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (430 mg), there was obtained the title compound (204 mg) as a white solid after addition of 2 ml of 2N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 40/60). m.p.= 208-210°C; ^{1}H-NMR (DMSO d-6): 0.67 (d, 3H, J= 6.6 Hz), 0.71 (d, 3H, J= 6.6 Hz), 0.89 (s, 9H), 0.90 (m, 1H), 1.23 (m, 1H), 1.41 (m, 1H), 2.56 (d, 3H, J= 4.4 Hz), 2.70 (m, 1H), 3.69 (m, 1H), 4.14 (d, 1H, J= 9.1 Hz), 7.35 (d, 1H, J= 9.1 Hz), 7.76 (t, 1H, J= 7.7 Hz), 7.90 (m, 1H), 7.99 (d, 1H, J= 8.8 Hz), 8.27 (d, 1H, J= 7.7 Hz), 8.33 (d, 1H, J= 6.3 Hz), 8.39 (d, 1H, J= 7.7 Hz), 8.57 (s, 1H), 8.71 (d, 1H, J= 6.3 Hz), 9.45 (s, 1H), 10.60 (s, 1H); MS (ESI): 522 (M + H$^+$).

The starting material was prepared as follows: In a manner analogous to that described in Example 1 (v) except that the reaction mixture was directly purified by flash chromatography on silica gel after evaporation of the solvents, from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxy-succinyl]-L-tert-leucine-N^1-methylamide (500 mg, 1.34 mmol) and isoquinoline-5-sulfonyl chloride (500 mg), there was obtained N^2-[2R-isobutyl-3S-(isoquinoline-5-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (580 mg, 77%) as a white foam. MS (ESI): 585 (M + Na$^+$). This (550 mg), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(isoquinoline-5-sulfonylamino)-succinyl]-L-tert-leucine-N^1-methylamide (450 mg) as a white solid; MS (ESI): 507 (M + H$^+$).

Example 18

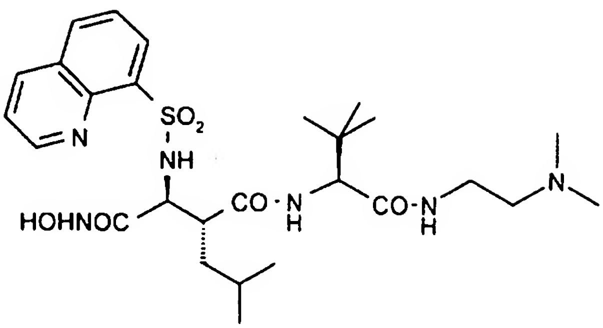
N²-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(1,2,3,4-tetrahydroquinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N¹-methylamide



A solution of N²-[4-(N-hydroxyamino)-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N¹-methylamide (250 mg, 0.48 mmol) in methanol (20 ml) was stirred under an atmosphere of hydrogen (50 PSI) in the presence of 10% palladium on charcoal (100 mg) for 5 hours. The solids were filtered off and the solvents were evaporated in vacuo. The residue was purified by C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 45/55). Evaporation of the solvents and trituration of the residue with ether yielded the title compound (211 mg; yield: 84%): ¹H-NMR (DMSO d-6): 0.74 (m, 6H), 0.78 (m, 1H), 0.90 (s, 9H), 1.25 (m, 1H), 1.39 (m, 1H), 1.81 (m, 2H), 2.56 (d, 3H, J= 4.4 Hz), 2.69 (m, 3H), 3.30 (m, 2H), 3.59 (m, 1H), 4.13 (d, 1H, J= 9.2 Hz), 5.96 (s, 1H), 6.47 (t, 1H, J= 7.7 Hz), 7.04 (d, 1H, J= 7 Hz), 7.32 (d, 1H, J= 7 Hz), 7.40 (m, 2H), 7.85 (m, 1H), 8.70 (s, 1H), 10.50 (s, 1H); MS (ESI): 548 (M + Na⁺).

Example 19

N²-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N¹-(dimethylamino)ethylamide



In a manner analogous to that described in the first paragraph of Example 1, except that that hydroxylamine hydrochloride and 2,6 lutidine were replaced by O-(tert-butyldimethylsilyl)-hydroxylamine (101 mg), from N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-8-sulfonylamino)-succinyl]-L-tert-leucine-N^1-(dimethylammonium)ethylamide trifluoroacetate (298 mg, 0.53 mmol), there was obtained the title compound (50 mg, 16%) as a white solid after addition of 1 ml of 1N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/ 1%AcOH (gradient from 0/100 to 40/60); ^{1}H-NMR (DMSO d-6): 0.63 (m, 6H), 0.86 (s, 9H), 0.90 (m, 1H), 1.3-1.0 (m, 2H), 2.49 (s, 6H), 2.60 (m, 2H), 2.80 (m, 1H), 3.20 (m, 2H), 3.80 (m, 1H), 4.10 (d, 1H, J= 9.2 Hz), 7.30 (m, 1H), 7.68 (m, 2H), 7.80 (m, 1H), 8.0 (m, 1H), 8.16 (m, 1H, J= 9.5 Hz), 8.22 (d, 1H, J= 9.5 Hz), 8.50 (m, 2H), 9.04 (m, 1H), 10.47 (m, 1H); MS (ESI): 579 (M + H^+).

The starting material was prepared as follows:

(i) To a solution of 3(R/S)-amino-2R-isobutylbutan-1,4-dioic acid-4 tert-butyl ester (1 g, 4.1 mmol) in acetonitrile (32 ml) was successively added quinoline-8-sulfonyl chloride (1.2 g, 5.3 mmol) and triethylamine (1.4 ml). The mixture was heated at 40-45°C for 20 minutes and cooled to room temperature. The solvents were evaporated in vacuo. The residue was dissolved in ethyl acetate and acidified with hydrochloric acid. The organic layer was dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 45/55 to 70/30) to yield 3R-(quinoline-8-sulfonylamino)-2R-isobutylbutan-1,4-dioic acid-4-tert-butyl ester. Further elution yielded 3S-(quinoline-8-sulfonylamino)-2R-isobutylbutan-1,4-dioic acid-4-tert-butyl ester (942 mg). ^{1}H-NMR ($CDCl_3$): 0.89 (d, 3H, J= 6.2 Hz), 0.91 (d, 3H,

J= 6.2 Hz), 0.94 (s, 9H), 1.8-1.4 (m, 3H), 3.06 (m, 1H), 4.40 (s br, 1H), 7.59 (m, 2H), 8.03 (d, 1H, J= 8.4 Hz), 8.25 (d, 1H, J= 8.4 Hz), 8.37 (d, 1H, J= 7.3 Hz), 9.09 (m, 1H)

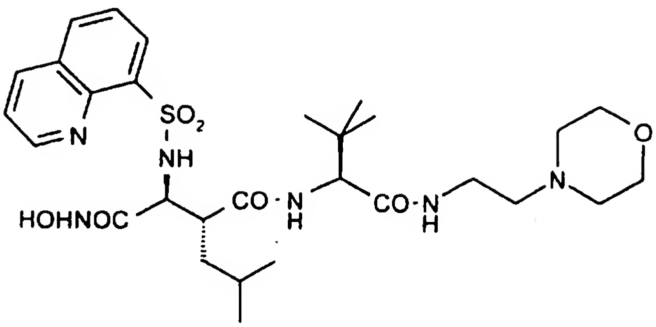
(ii) To a solution of 3S-(quinoline-8-sulfonylamino)-2R-isobutylbutan-1,4-dioic acid-4-tert-butyl ester (225 mg, 0.52 mmol) in DMF (1.5 ml) at 0°C was added successively 1-hydroxybenzotriazole (84 mg, 0.62 mmol), L-tert-leucine dimethylaminoethylamide(Note) (114 mg, 0.57 mmol), DMAP (63 mg, 0.52 mmol), and N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (118 mg, 0.62 mmol). The mixture was stirred at room temperature for eighteen hours. The solvents were evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine and dried over $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by flash chromatography on silica using acetone-dichloromethane (gradient from 0:100 to 50:50) as eluant to give N^2-[2R-isobutyl-3S-(quinoline-8-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-(dimethylamino)ethylamide (218 mg, 61%) as a white foam. MS (ESI): 620 ($M + H^+$).

(iii) In a manner analogous to that described in Example 1 (vi), from N^2-[2R-isobutyl-3S-(quinoline-8-sulfonyl)amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-(dimethylamino)-ethylamide (220 mg, 0.40 mmol), there was obtained N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-(dimethylammonium)ethylamide trifluoroacetate (194 mg, 91%) as a solid; MS (ESI): 564 ($M + H^+$).

(Note) L-tert-leucine dimethylaminoethylamide was prepared by the reaction of L-tert-leucine with triphosgene to give 3-(S)-tert-butyloxazolidine-1,4-dione which was then treated with N,N-dimethylethylenediamine.

Example 20

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-morpholinoethylamide



In a manner analogous to that described in the first paragraph of Example 1, except that hydroxylamine hydrochloride and 2,6 lutidine were replaced by O-(tert-butyldimethylsilyl)-hydroxylamine (102 mg), from N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-8-sulfonylamino)-succinyl]-L-tert-leucine-N^1-morpholinoethylamide (210 mg, 0.347 mmol), there was obtained the title compound as a white solid after addition of 1 ml of 1N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and 0.2% aqueous ammonium carbonate (gradient from 0/100 to 40/60); ^{1}H-NMR (DMSO d-6 + TFA d-1): 0.66 (m, 6H), 0.86 (s, 9H), 0.90 (m, 1H), 1.25 (m, 2H), 2.90 (m, 1H), 3.15 (m, 4H), 3.43 (m, 4H), 3.67 (m, 2H), 3.82 (d, 1H, J= 8.8 Hz), 4.0 (m, 3H), 7.70 (m, 2H), 8.20 (m, 1H), 8.25 (d, 1H, J= 7.8 Hz), 8.51 (d, 1H, J= 8.3 Hz), 9.04 (m, 1H); MS (ESI): 621 (M + H^+).

The starting material was prepared as follows:

(i) To a solution of 3S-(quinoline-8-sulfonylamino)-2R-isobutylbutan-1,4-dioic acid-4-tert-butyl ester (370 mg, 0.85 mmol) in DMF (2.5 ml) at 0°C was added successively 1-hydroxybenzotriazole (137 mg, 1.02 mmol), L-tert-leucine morpholinoethylamide[(Note)] (227 mg, 0.93 mmol), DMAP (103 mg, 0.85 mmol) and N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (194 mg, 1.02 mmol). The mixture was stirred at room temperature for eighteen hours. The solvents were evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, dried over $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by flash chromatography on silica using acetone-dichloromethane (gradient from 50:50 to 100:0) as eluant to give N^2-[2R-isobutyl-3S-(quinoline-8-

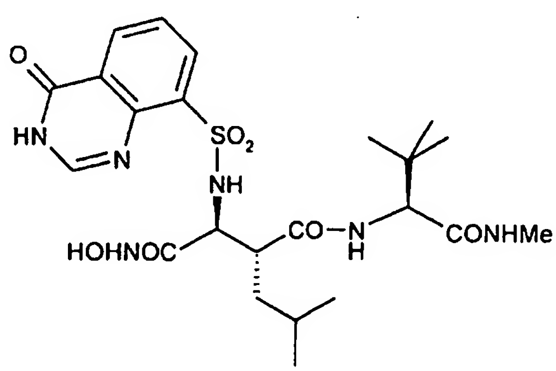
sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N'-morpholinoethylamide (400 mg, 71%) as a white foam. MS (ESI): 662 (M + H^+).

(ii) In a manner analogous to that described in Example 1 (vi), from N^2-[2R-isobutyl-3S-(quinoline-8-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N'-morpholinoethylamide(400 mg, 0.60 mmol), there was obtained N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N'-morpholinoethylamide (159 mg) as a solid after evaporation of the solvent and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and 0.2% aqueous ammonium carbonate (gradient from 40/60 to 50/50). MS (ESI): 606 (M + H^+).

(Note) L-tert-leucine morpholinoethylamide was prepared by the reaction of L-tert-leucine with triphosgene to give 3-(S)-tert-butyloxazolidine-1,4-dione which was then treated with morpholinoethylamine.

Example 21

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-8-sulfonylamino)succinyl]-L-tert-leucine-N'-methylamide



In a manner analogous to that described in the first paragraph of Example 1, except that no 1-hydroxybenzotriazole was added and that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)hydroxylamine (135 mg), from N^2-[4-hydroxy-2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-8-sulfonylamino)succinyl]-L-tert-leucine-N'-methylamide (240 mg, 0.46 mmol), there was obtained the title compound (158 mg, 64%) as a

solid after addition of 2 ml of 2N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 45/55); ^{1}H-NMR (DMSO d-6): 0.71 (m, 6H), 0.89 (s, 9H), 0.90 (m, 1H), 1.25 (m, 1H), 1.35 (m, 1H), 2.56 (d, 3H, J= 4.4 Hz), 3.76 (m, 1H), 4.17 (d, 1H, J= 9.2 Hz), 7.14 (d, 1H, J= 9.9 Hz), 7.59 (t, 1H, J= 7.9 Hz), 7.76 (d, 1H, J= 9.5 Hz), 7.84 (m, 1H), 8.16 (d, 1H, J= 7.9 Hz), 8.24 (s, 1H), 8.31 (d, 1H, J= 7.9 Hz), 8.48 (s, 1H), 10.44 (s, 1H); MS (ESI): 539 (M + H^+).

The starting material was prepared as follows:

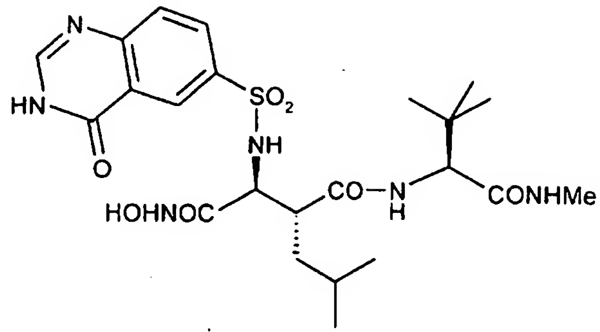
(i) In a manner analogous to that described in Example 1 (v), from N^2-[2R-isobutyl-3S-amino-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (750 mg, 1.34 mmol) and a mixture [(Note)] of 4-oxo-3,4-dihydroquinazoline-6-sulfonyl chloride and 4-oxo-3,4-dihydroquinazoline-8-sulfonyl chloride (1.5 g, 1:1), there was obtained N^2-[2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-8-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (332 mg) as a foam (MS (ESI): 602 (M + Na^+)) and N^2-[2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-6-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (428 mg) after purification on HPLC using ethyl acetate as eluant (MS (ESI): 602 (M + Na^+)).

(ii) In a manner analogous to that described in Example 1 (vi), from N^2-[2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-8-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (300 mg, 0.51 mmol), there was obtained N^2-[4-hydroxy-2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (260 mg) as a solid. MS (ESI): 524 (M + H^+).

[(Note)] Prepared by reaction of 3,4-dihydroquinazolin-4-one with chlorosulfonic acid

Example 22

N^2-[4-(N-hydroxyamino)-2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-6-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide



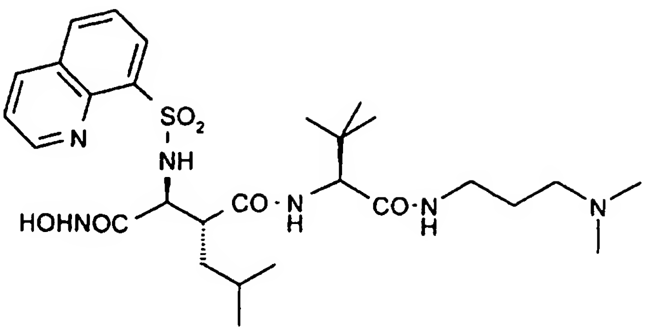
In a manner analogous to that described in the first paragraph of Example 1, except that no 1-hydroxybenzotriazole was added and that hydroxylamine hydrochloride and 2,6-lutidine were replaced by O-(tert-butyldimethylsilyl)hydroxylamine (191 mg), from N^2-[4-hydroxy-2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-6-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (340 mg, 0.65 mmol), there was obtained the title compound (195 mg, 56%) as a solid after addition of 2 ml of 2N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 0/100 to 45/55); ^{1}H-NMR (DMSO d-6): 0.73 (m, 6H), 0.88 (s, 9H), 0.90 (m, 1H), 1.27 (m, 1H), 1.43 (m, 1H), 2.56 (d, 1H, J= 4.4 Hz), 2.67 (m, 1H), 3.67 (m, 1H), 4.11 (d, 1H, J= 9.2 Hz), 7.21 (d, 1H, J= 9.5Hz), 7.75 (d, 1H, J= 8.5 Hz), 7.85 (m, 2H), 8.02 (dd, 1H, J= 8.5 Hz, J'= 2.2 Hz), 8.24 (s, 1H), 8.44 (s, 1H), 10.74 (s, 1H); MS (ESI): 539 ($M + H^+$).

The starting material was prepared as follows:

(i) In a manner analogous to that described in Example 1 (vi), from N^2-[2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-6-sulfonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (400 mg, 0.69 mmol), [see Example 21] there was obtained N^2-[4-hydroxy-2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-6-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide (360 mg) as a solid. MS (ESI): 524 ($M + H^+$).

Example 23

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(quinoline-8-sulphonylamino)succinyl]-L-tert-leucine-N^1-(dimethylamino)propylamide



In a manner analogous to that described in the first paragraph of Example 1, except that hydroxylamine hydrochloride was replaced by O-(tert-butyldimethylsilyl)hydroxylamine (102 mg), from N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-8-sulphonylamino)succinyl]-L-tert-leucine-N^1-(dimethylammonium)propylamide trifluoroacetate (200 mg, 0.32 mmol), there was obtained the title compound (60 mg, 29%) as a white solid after addition of 1 ml of 1N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 10/90 to 40/60). ^{1}H-NMR (D_2O): 0.7 (d, 3H, J = 6.6 Hz), 0.72 (d, 3H, J = 6.6 Hz), 1.02 (m, 1H), 1.06 (s, 9H), 1.2-1.36 (m, 2H), 1.95 (m, 2H), 2.86 (m, 1H), 2.88 (s, 6H), 3.15 (m, 2H), 3.31 (m, 2H), 3.81 (d, 1H, J = 9.5 Hz), 4.2 (s, 1H), 7.74 (m, 1H), 7.8 (m, 1H), 8.32 (d, 1H, J= 8.0 Hz), 8.38 (dd, 1H, J= 7.3 Hz, J = 1.5 Hz), 8.53 (dd, 1H, J= 8.4 Hz, J = 1.5 Hz), 9.07 (dd, 1H, J= 4.4 Hz, J = 1.5 Hz); MS (ESI) : 593 (M + H^+).

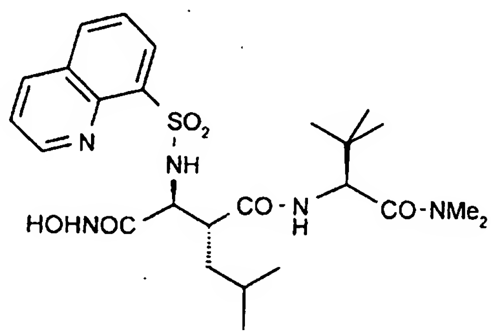
The starting material was prepared as follows:

In a manner analogous to that described in Example 19 ii), from 3S-(quinolin-8-yl)sulphonylamino-2R-isobutylbutan-1,4-dioic acid 4-tert-butyl ester (330 mg, 0.75 mmol) and L-tert-leucine dimethylaminopropylamide[(Note)] (179 mg, 0.83 mmol) there was obtained N^2-[2R-isobutyl-3S-(quinoline-8-sulphonylamino)- 4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-(dimethylamino)propylamide (258 mg, 54%) as a white solid; MS (ESI): 634 (M + H^+). This (250 mg, 0.4 mmol), in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-(dimethylammonium)propylamide trifluoroacetate (220 mg, 97%) as a white powder. MS (ESI): 578 (M + H^+).

(Note) L-tert-leucine dimethylaminopropylamide was prepared by the reaction of L-tert-leucine with triphosgene to give 3-(S)-tert-butyloxazolidine-1,4-dione which was then treated with N,N-dimethylpropylenediamine.

Example 24

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(quinoline-8-sulphonylamino)succinyl]-L-tert-leucine-N^1-dimethylamide



In a manner analogous to that described in the first paragraph of Example 1, except that that hydroxylamine hydrochloride was replaced by O-(tert-butyldimethylsilyl)hydroxylamine (94 mg), from N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-8-sulphonylamino)succinyl]-L-tert-leucine-N^1-dimethylamide (280 mg, 0.54 mmol), there was obtained the title compound (140 mg, 49%) as a white solid after addition of 0.5 ml of 1N hydrochloric acid to the crude mixture at the end of the reaction and purification of this mixture on C18 preparative HPLC using as eluant a mixture of methanol and water/1%AcOH (gradient from 20/80 to 50/50). ^{1}H-NMR (D_2O): 0.66 (d, 3H, J = 6.2 Hz), 0.68 (d, 3H, J = 6.2 Hz), 1.04 (s, 9H), 1.07 (m, 1H), 1.1-1.28 (m, 2H), 2.83 (m, 1H), 2.94 (s, 3H), 3.22 (s, 3H), 3.84 (d, 1H, J = 9.2 Hz), 4.91 (d, 1H, J = 9.2 Hz), 7.75-7.8 (m, 2H), 8.18 (d, 1H, J = 8.8Hz), 8.31 (d, 1H, J= 8.2 Hz), 8.38 (dd, 1H, J= 7.3 Hz, J = 1.5 Hz), 8.51 (dd, 1H, J= 8.4 Hz, J = 1.5 Hz), 9.07 (dd, 1H, J= 4.4 Hz, J = 1.5 Hz); MS (ESI) : 536 (M + H$^+$) and 558 (M + Na$^+$).

The starting material was prepared as follows:

In a manner analogous to that described in Example 19 (ii), from 3S-(quinoline-8-sulphonyl-amino)-2R-isobutylbutan-1,4-dioic acid 4-tert-butyl ester (295 mg, 0.67 mmol) and L-tert-leucine dimethylamide(Note) (118 mg, 0.74 mmol) there was obtained N^2-[2R-isobutyl-3S-

(quinoline-8-sulphonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-dimethylamide (339 mg, 87%) as a white solid. MS (ESI): 577 ($M + H^+$) and 599 ($M + Na^+$).

This, in a manner analogous to that described in Example 1 (vi), was converted to N^2-[4-hydroxy-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-dimethylamide (280 mg, 97%) as a white powder; MS (ESI): 521 ($M + H^+$).

(Note) L-tert-leucine dimethylamide was prepared by the reaction of L-tert-leucine with triphosgene to give 3-(S)-tert-butyloxazolidine-1,4-dione which was then treated with a saturated solution of dimethylamine.

Example 25

A number of compounds were prepared by solid phase synthesis according to the following general procedure.

A gas dispersion tube (with N^2-[2R-isobutyl-3S-amino-4-(N-oxyamino)succinyl]-L-tert-leucine-N^1-methylamide linked via the oxygen atom of the N-oxyamino group to SASRIN resin (100 mg, ca 0.05 mmol) inside) was placed in a test tube and 25% pyridine in dichloromethane (3 ml, v/v) was added, followed by a sulfonyl chloride (0.3 mmol) in dichloromethane (1 ml). The mixture was agitated in a sonicated bath for 2 hours. The gas dispersion tube was drained and sparged with nitrogen. The standard protocol for washing the resin consisted in adding dichloromethane (2x6 ml), methanol (2x6 ml) and dichloromethane (2x6 ml) into the gas dispersion tube, followed by agitation by sonication for 5 minutes, and finally draining by gravity and sparging with nitrogen.

To the resin in a gas dispersion tube (itself placed in a test tube) was added 5% trifluoroacetic acid in dichloromethane (5 ml). The mixture was agitated in a sonicated bath for 15 minutes. The resin was drained, sparged with nitrogen, washed with methanol (3 ml), drained and sparged with nitrogen. The filtrates were concentrated in vacuo to give the desired product of this invention. The mass spectrum (ESI) was recorded. The retention time was measured on (125/4.6 mm Kromasil C18, 5 µm HPLC, eluant: methanol and water/1%AcOH; linear gradient from 30:70 to 90:10 for 10 minutes then 100:0 for 5 minutes; flow rate 1.5 ml/mn, UV detection 254 nm and light diffusion detection).

N^2-[2R-Isobutyl-3S-amino 4-(N-oxyamino)succinyl]-L-tert-leucine-N^1-methylamide loaded on SASRIN resin was prepared as follows:

(i) To a solution of 3(R/S)-amino-2R-isobutylbutan-1,4-dioic acid-4-tert-butyl ester (4.7 g, 19.1 mmol, R/S 1:3 mixture) in a mixture of dioxane (50 ml) and 10% aqueous sodium carbonate (100 ml) cooled at 0°C was added a solution of 9-fluorenylmethyl chloroformate (5 g, 19.3 mmol) in dioxane (80 ml) dropwise. The mixture was warmed to room temperature and stirred for one hour. The mixture was acidified to pH 3 by addition of 4N hydrochloric acid, extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and the solvents were evaporated in vacuo to give 3(R/S)-(9-fluorenylmethoxycarbonylamino)-2R-isobutylbutan-1,4-dioic acid-4-tert-butyl ester as a white solid.

(ii) To a solution of crude 3(R/S)-(9-fluorenylmethoxycarbonylamino)-2R-isobutylbutan-1,4-dioic acid-4-tert-butyl ester in dichloromethane (70 ml) was added L-tert-leucine methylamide (3.8 g), and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.4 g, 23.0 mmol). The mixture was stirred for 3 hours, diluted with ethyl acetate, washed with 1N hydrochloric acid and brine. The organic layer was dried over $MgSO_4$. The residue was purified by chromatography on silica gel using dichloromethane/acetonitrile (85:15) as eluant to give N^2-[2R-isobutyl-3S-(9-fluorenylmethoxycarbonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (4.0 g) as a white foam.
^{1}H-NMR ($CDCl_3$): 0.93 (d, 6H, J= 6.3 Hz), 1.00 (s, 9H), 1.44 (s, 9H), 1.7-1.4 (m, 3H), 2.82 (d, 3H, J= 4.8 Hz), 2.99 (m, 1H), 4.14 (d, 1H, J= 9.2 Hz), 4.50-4.20 (m, 4H), 5.70 (m, 1H), 6.40 (m, 2H), 7.30 (m, 2H), 7.39 (m, 2H), 7.63 (m, 2H), 7.76 (m, 2H).

(iii) To a solution of N^2-[2R-isobutyl-3S-(9-fluorenylmethoxycarbonylamino)-4-tert-butyloxysuccinyl]-L-tert-leucine-N^1-methylamide (4 g, 6.74 mmol) in dichloromethane (20 ml) was added trifluoroacetic acid (20 ml). The mixture was stirred for 18 hours at 0°C. The solvents were evaporated in vacuo. The residue was taken up in toluene and the solvent was removed in vacuo (three times). The residue was triturated in a mixture of pentane/ether (1:1) to give white crystals which were collected and dried in vacuo to yield N^2-[2R-isobutyl-3S-(9-fluorenylmethoxycarbonylamino)-4-hydroxysuccinyl]-L-tert-leucine-N^1-methylamide (3.6 g).

^1H-NMR (DMSO d-6): 0.83 (m, 15H), 1.10 (m, 1H), 1.37 (m, 1H), 1.52 (m, 1H), 2.56 (d, 3H, J= 4.4 Hz), 2.97 (m, 1H), 3.97 (m, 1H), 4.35-4.10 (m, 4H), 7.90-7.10 (m, 11H)

(iv) 4-(Hydroxymethyl)-2-methoxyphenoxymethyl-copoly(styrene-1%divinylbenzene)-resin (SASRIN resin)[(Note)] (2.6 g, ca 0.7 mmol/g loading, 1.8 mmol) was suspended in dry chloroform (100 ml) and gently agitated for 30 minutes under a blanket of argon. N-hydroxyphthalimide (2.71 g, 16.6 mmol) and triphenylphosphine (4.36 g, 16.6 mmol) were added. The mixture was stirred for 15 minutes. Diethylazodicarboxylate (2.6 ml, 16.6 mmol) was added dropwise and the mixture was shaken for 72 hours. The resin was collected by filtration, washed successively with chloroform (3x100 ml), methanol (3x100 ml), dichloromethane (3x100 ml), ether (3x100 ml) and dried.
^{13}C NMR (gel in $CDCl_3$): 55.4, 69.7, 74.2, 99.1, 163.4; IR: 1730

[(Note)] Prepared from chloromethyl-copoly(styrene-1%divinylbenzene)-resin (Merrifield resin, supplied by Bachem, loading: 0.8-1 mmol/g) according to Mergler M, Tanner R, Gosteli J, Grogg P, Tetrahedron Lett., 1988, 29, 4005

(v) The resin described in (iv) (3.6 g, ca 0.6 mmol/g) was suspended in methanol (100 ml) for 30 mn. To this mixture was added hydrazine hydrate (0.77 ml, 15.8 mmol). The mixture was stirred at room temperature for 18 hours. The resin was collected by filtration, washed successively with methanol (3x100 ml), dichloromethane (3x100 ml), ethyl acetate (3x100 ml) ether (3x100 ml) and dried to give 4-(aminoxymethyl)-2-methoxyphenoxymethyl-copoly(styrene-1%divinylbenzene)-resin. (Estimation of the loading was assessed by dosing the liberated phthalhydrazide: 0.5-0.7 mmol/g)
^{13}C NMR (gel in THF d-8): 58.1, 73.0, 75.4, 102.2

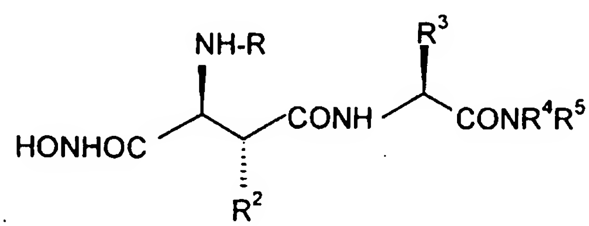
(vi) 4-(Aminoxymethyl)-2-methoxyphenoxymethyl-copoly(styrene-1%divinylbenzene)-resin (7.5 g, ca 0.5 mmol/g loading, 3.75 mmol) was suspended in DMF (200 ml) and gently agitated for 30 minutes. To this slurry was successively added N^2-[2R-isobutyl-3S-(9-fluorenylmethoxycarbonylamino)-4-hydroxysuccinyl]-L-tert-leucine-N^1-methylamide (2.62 g, 4.88 mmol), N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.6 g, 18.8

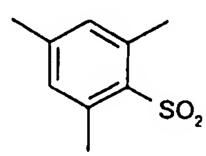
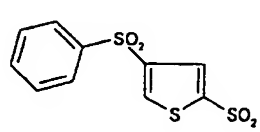
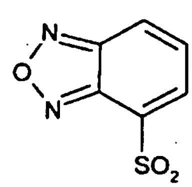
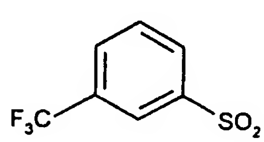
mmol) and DMAP (600 mg). The mixture was shaken for 72 hours and the resin was collected by filtration, washed successively with DMF (2x100 ml), dichloromethane (100 ml), methanol (2x100 ml), dichloromethane (100 ml), ether (100 ml) and dried.

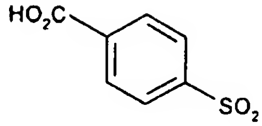
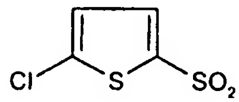
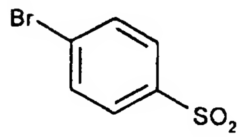
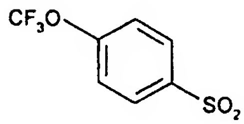
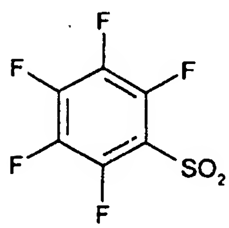
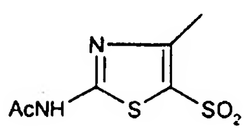
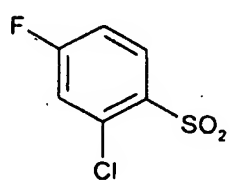
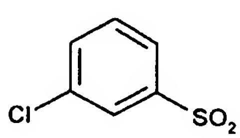
(FMOC group deprotection)

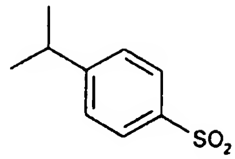
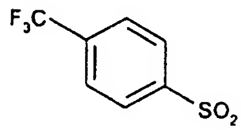
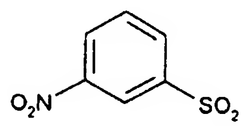
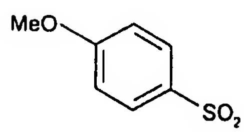
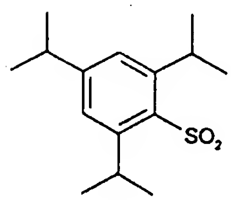
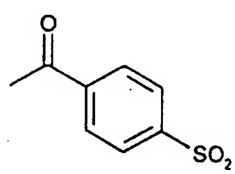
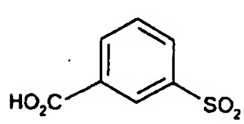
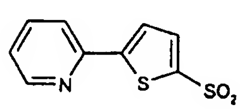
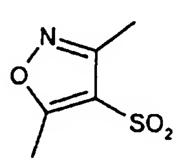
The resin was shaken with a solution of 25% piperidine in DMF (v/v, 200 ml) for 4 hours. The resin was collected by filtration, washed with DMF (2x100 ml), methanol (2x100 ml), dichloromethane (2x100 ml), ether (100 ml) and dried to give 8.65 g of SASRIN resin grafted with N[2]-[2R-isobutyl-3S-amino 4-(N-oxyamino)succinyl]-L-tert-leucine-N[1]-methylamide.

Compounds of the formula prepared by the general procedure of Example 25:



Compound	R	MS(M+H+)	Retention time (mins)
a		513	9.8
b		617	8.6
c		513	7.5
d		539	9.0

e		515	6.6
f		511	8.6
g		549	8.8
h		555	9.3
i		561	9.5
j		549	7.0
k		523	8.0
l		505	8.5

m		513	9.8
n		539	9.2
o		516	7.9
p		501	7.3
q		597	12.6
r		513	
s		515	
t		554	8.2
u		490	7.2

Yields were in the range 11-23 mg.

Example 26

Typical tablet formulations for a compound of this invention or a pharmaceutically-acceptable salt thereof ('Compound X') are:

(a) Tablet Formulation I

Tablet Formulation I	mg/tablet
Compound X	100
Lactose Ph.Eur	179
Croscarmellose sodium	12
Polyvinylpyrrolidone	6
Magnesium stearate	3

(b) Tablet Formulation II

Tablet Formulation II	mg/tablet
Compound X	250
Lactose Ph.Eur	215
Croscarmellose sodium	20
Polyvinylpyrrolidone	10
Magnesium stearate	5

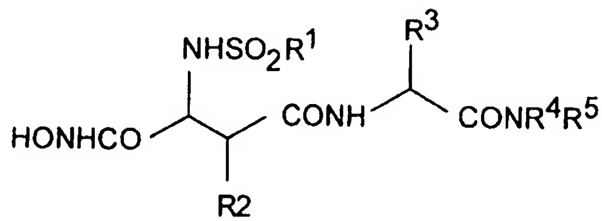
The tablets may be prepared by conventional procedures well known in the pharmaceutical art and may be film coated with typical coating materials such as hydroxypropylmethylcellulose.

FS70186

PMD/MB : 24JUL97

CLAIMS

1. A compound of the formula (I):



(I)

wherein:

R^1 is aryl, heterocyclyl or heteroaryl;

R^2 is hydrogen, C_{1-8}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, heteroaryl, heterocyclyl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, heterocyclylC_{1-6}alkyl or C_{3-8}cycloalkylC_{1-6}alkyl;

R^3 is C_{1-6}alkyl, C_{2-6}alkenyl, aryl, C_{1-6}alkyl, heteroarylC_{1-6}alkyl or the side-chain of a naturally occurring amino acid;

R^4 is hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{4-8}cycloalkenyl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl or heterocyclylC_{1-6}alkyl;

R^5 is hydrogen or C_{1-6}alkyl; or R^4 and R^5 together with the nitrogen atom to which they are joined form a heterocyclic ring;

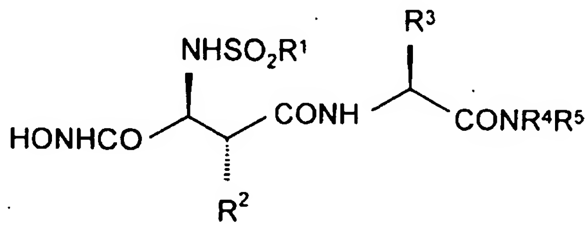
wherein any group or ring, in R^1-R^5, is optionally substituted; or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof.

2. A compound according to claim 1 wherein R^1 is phenyl or naphthyl wherein either is unsubstituted or substituted by one or two groups selected from halo, C_{1-6}alkylcarbonyl, C_{1-6}alkanoylamino, trifluoromethyl, cyano, C_{1-6}alkyl, trifluoromethoxy, carboxy, nitro, di-C_{1-6}alkylamino and C_{1-6}alkoxy.

3. A compound according to claim 1 wherein R^1 is pyridazinyl, pyrimidinyl, pyridinyl, triazolyl, imidazolyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl or isoxazolyl, any of which is optionally substituted by C_{1-6}alkyl, halo, phenyl or pyridyl.

4. A compound according to claim 1 wherein R^1 is quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, quinazolinyl, 3,4-dihydroquinazolinyl, indolyl, benzofuranyl, benzthiazolyl, benzofurazanyl or isoindolyl, any of which is optionally substituted by C_{1-6}alkyl or oxo.

5. A compound according to any one of claims 1 to 4 which is of the formula (II):



(II)

wherein:

R^1 is phenyl or naphthyl either being unsubstituted or substituted by one or two groups selected from halogen;

C_{1-6}alkylcarbonyl, C_{1-6}alkanoylamino, trifluoromethyl, cyano, C_{1-6}alkyl, trifluoromethoxy, carboxy, nitro, di-C_{1-6}alkylamino or C_{1-6}alkoxy;

or R^1 is pyridazinyl, pyrimidinyl, pyridinyl, triazolyl, imidazolyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl or oxazolyl any of which is unsubstituted or substituted by C_{1-6}alkyl, halo, phenyl or pyridinyl;

or R^1 is quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, quinazolinyl, 3,4-dihydroquinazolinyl, indolyl, benzofuranyl, benzothiazolyl, benzofurazanyl or isoindolyl any of which is unsubstituted or substituted by C_{1-6}alkyl and/or oxo (= O);

R^2 is isobutyl;

R^3 is isobutyl, tert-butyl, 1,1-dimethylmethylthiomethyl or benzyl;

R^4 is methyl, ethyl, n-propyl, isobutyl, tert-butyl, dimethylaminoethyl, dimethylaminopropyl, 2-morpholinoethyl or benzyl; and R^5 is hydrogen or methyl; or R^4 and R^5 together with the nitrogen atom to which they are joined form a morpholine ring.

6. A compound according to claim 1 which is:

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-benzenesulfonylaminosuccinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(naphthalene-2-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-acetamidobenzenesulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(naphthalene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(1-methylimidazole-4-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophene-2-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3,5-dichlorobenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-fluorobenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-cyanobenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-pyridinesulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-6-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(5-dimethylaminonaphthalene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tert-butylbenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-hydroxyamino)-2R-isobutyl-3S-(oxindole-5-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-hydroxyamino)-2R-isobutyl-3S-(quinoline-6-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(isoquinoline-5-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(1,2,3,4-tetrahydroquinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-(dimethylamino)ethylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(quinoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-morpholinoethylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-8-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-hydroxyamino)-2R-isobutyl-3S-(4-oxo-3,4-dihydroquinazoline-6-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(quinoline-8-sulphonylamino)succinyl]-L-tert-leucine-N^1-(dimethylamino)propylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(quinoline-8-sulphonylamino)succinyl]-L-tert-leucine-N^1-dimethylamide;

N^2-[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-acetylbenzene-1-sulfonylamino)succinyl]-L-tert-leucine-N^1-methylamide;

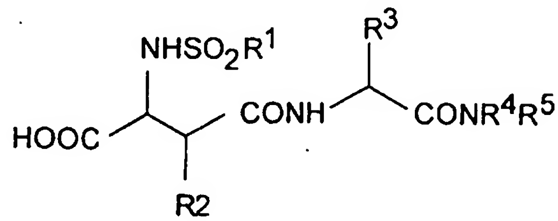
or a pharmaceutically-acceptable salt thereof.

7. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 6 or pharmaceutically acceptable salt or in vivo hydrolysable ester thereof and a pharmaceutically acceptable carrier.

8. The use of a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for the manufacture of a medicament for treating disease conditions mediated by TNF.

9. A process for preparing a compound according to claim 1 or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof which process comprises

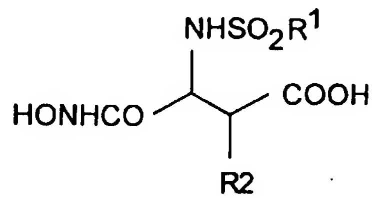
a) reacting a compound of the formula (III):



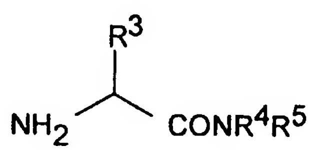
(III)

wherein R^1-R^5 are as defined in claim 1. or an activated derivative thereof with hydroxylamine, O-protected hydroxylamine or a salt thereof; or

b) coupling a compound of the formula (IV) with a compound of the formula (V):



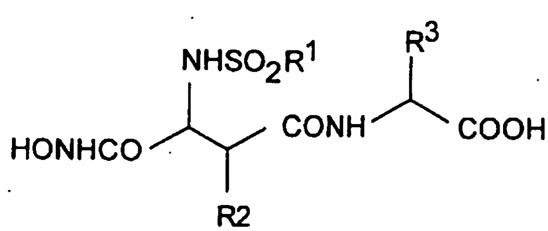
(IV)



(V)

wherein R^1-R^5 are as defined in claim 1; or

c) reacting a compound of the formula (VI) with compound of the formula (VII):



(VI)

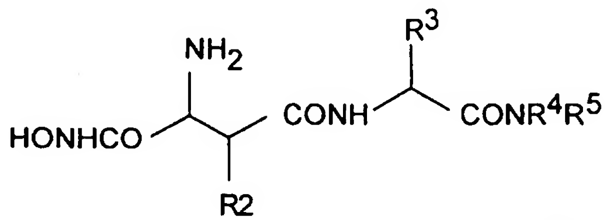
$$NHR^4R^5$$

(VII)

wherein R^1-R^5 are as defined in claim 1;

or

d) reacting a compound of the formula (VIII) with a compound of the formula (IX):



(VIII)

$$R^1SO_2X$$

(IX)

wherein R^1-R^5 are as defined in claim 1 and X is a leaving group;

wherein any functional group is protected, if necessary, and:

i. removing any protecting groups;

ii. optionally forming a pharmaceutically acceptable salt or <u>in vivo</u> hydrolysable ester.

10. A compound of the formula (III) as defined in claim 9.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 97/02222

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/06 C07C311/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 20047 A (BRITISH BIO TECHNOLOGY ;CRIMMIN MICHAEL JOHN (GB); GALLOWAY WILLIA) 14 October 1993 see claim 1; example 14 ---	1-9
Y	WO 96 00214 A (CIBA GEIGY AG ;MACPHERSON LAWRENCE JOSEPH (US); PARKER DAVID THOMA) 4 January 1996 see claim 1 ---	1-9
Y	WO 94 10900 A (RES DEV FOUNDATION) 26 May 1994 see claim 1 -----	1-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 1997	13. 11. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Deffner, C-A

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/GB 97/02222

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9320047 A	14-10-93	AT 150452 T	15-04-97
		AU 3899193 A	08-11-93
		DE 69309047 D	24-04-97
		EP 0634998 A	25-01-95
		JP 7505387 T	15-06-95
		US 5525629 A	11-06-96
		ZA 9302501 A	08-11-93
WO 9600214 A	04-01-96	US 5506242 A	09-04-96
		AU 2536995 A	19-01-96
		CA 2192092 A	04-01-96
		EP 0766672 A	09-04-97
		FI 965156 A	20-12-96
		NO 965568 A	17-02-97
		US 5552419 A	03-09-96
		US 5646167 A	08-07-97
		US 5672615 A	30-09-97
		ZA 9505206 A	27-12-95
WO 9410900 A	26-05-94	AU 5593994 A	08-06-94
		CN 1089123 A	13-07-94
		US 5608472 A	04-03-97
		ZA 9308193 A	03-05-95